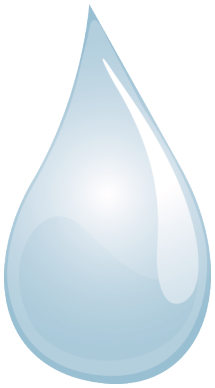
TOWARDS PATIENT CENTERED CARE IN FEMALE STRESS URINARY INCONTINENCE



Juliën Labrie

Towards patient centered care in female stress urinary incontinence

Thesis, University of Utrecht, the Netherlands

ISBN: 978-94-6182-527-8

Cover design: www.marcellabrie.nl

Layout and printing: Off Page

The PORTRET study was financially supported by ZonMW (grant number 80-82310-98-08203)

Printing of this thesis was financially supported by: Division Woman and Baby, University Medical Center Utrecht, ABN AMRO, Astellas, Bergman Vrouwenzorg, BMA BV (Mosos), Chipsoft, Ferring BV, Gilles Hondius Foundation, Goodlife, Johnson & Johnson Medical BV, Medical Dynamics, Memidis Pharma BV, Origio Benelux BV, Will Pharma, BARD, Dr. Falk Pharma BV and Zambon BV.

TOWARDS PATIENT CENTERED CARE IN FEMALE STRESS URINARY INCONTINENCE

Richting individuele zorg voor vrouwen met stressincontinentie
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op donderdag 22 januari 2015 des ochtends te 10.30 uur

door

Juliën Labrie
geboren op 28 januari 1983 te Rotterdam

Promotoren:	Prof. dr. C.H. van der Vaart
	Prof. dr. A.L.M. Lagro-Janssen
Copromotoren:	Dr. K. Fischer
	Dr. L.C.M. Berghmans

I am what I am.
I don't want praise, I don't want pity.
I bang my own drum.
Some think it's noise, I think it's pretty!

From: La cage aux folles, Jerry Herman; 1983
(Popularised by Dame Shirley Bassey)

Aan mijn ouders

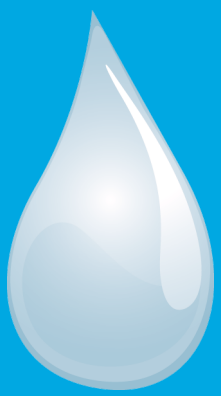


TABLE OF CONTENTS


1

GENERAL INTRODUCTION

INTRODUCTION

Urinary incontinence (UI) is a major health care problem, with a profound negative impact on Health Related Quality of Life (HRQoL).[1,2] Incontinent women should not be satisfied with using incontinence pads for the rest of their lives. They should seek appropriate treatment for their problems and need to be treated effectively. Unfortunately, only 10-20% of women with stress urinary incontinence will consult a doctor for their problems.[3–5] The current advice is to start with pelvic floor muscle training (physiotherapy) as initial treatment in all stress urinary incontinent women. The reported subjective and objective success rates of physiotherapy for women with moderate so severe stress urinary incontinence vary. After 3 to 15 years up to 50% of urinary incontinent women will have proceeded to midurethral slingsurgery (slingsurgery).[6–9] Slingsurgery has been researched extensively and is regarded as safe and effective. However, currently women can only undergo slingsurgery when physiotherapy falls short.[10–12] We questioned whether all women with stress incontinence should initially be treated with physiotherapy or if slingsurgery could be a good initial treatment option as well.

PREVALENCE OF URINARY INCONTINENCE

Various definitions of incontinence, measures to quantify urine leakage, severity of incontinence and different populations under study have been described.[13,14] As a result, a wide range in prevalence (the proportion of the population having a disease at a given point in time) of urinary incontinence has been reported in literature.[3,5] Overall, approximately 30-40% of adult women are affected by urinary incontinence. Stress urinary incontinence is the most common type of urinary incontinence and affects half of all incontinent women, resulting in a total prevalence of stress urinary incontinence of 20% in the female population. The prevalence of stress urinary incontinence varies within age groups and peaks in women between 40-49 years of age and decreases with older age. In the other half of incontinent women 40% experience urge urinary and 10% experience mixed urinary incontinence.[5]

In this dissertation the following internationally accepted definitions composed by the International Continence Society (ICS) for different forms of incontinence are used:[13]

- *Urinary incontinence (symptom):* Complaint of involuntary loss of urine
- *Stress Urinary Incontinence (SUI):* Complaint of involuntary loss of urine on effort or physical exertion (e.g., sporting activities), or on sneezing or coughing. ''Activity-related incontinence'' might be preferred in some languages to avoid confusion with psychological stress.
- *Urgency Urinary Incontinence (UUI):* Complaint of involuntary loss of urine associated with urgency.
- *Mixed Urinary Incontinence (MUI):* Complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing.

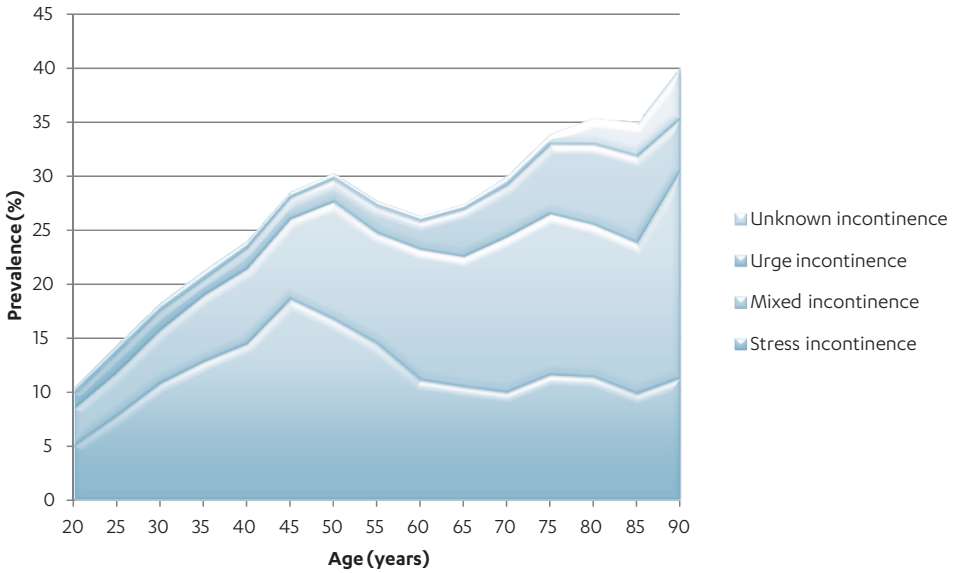


Figure 1. Prevalence of incontinence in community-dwelling women. EPINCONT study, Hannestad et al., compiled with permission from the authors.[5]

PATHOPHYSIOLOGY OF STRESS URINARY INCONTINENCE

The pathophysiological basis of stress urinary incontinence is not completely understood, but two mechanisms are widely accepted in the development of stress urinary incontinence: urethral hypermobility and Intrinsic Sphincter Deficiency (ISD).

The general theory is that leakage of urine from the urethra/bladder occurs when the intra-abdominal pressure (thus pressure in the bladder) exceeds the maximal urethral closing pressure. Enhörning first described this theory in 1961.[15] He theorised that adequate intra-abdominal pressure transmission could only be achieved if the bladder neck and proximal urethra were located in the correct anatomical position.

In 1994 DeLancey elaborated on this hypothesis that hypermobility of the urethra is a manifestation of a weakened support of the proximal urethra.[16] This theory is internationally known and accepted as: "The Hammock Theory". DeLancey described the urethra as resting on supportive tissue (the pubo-urethral ligament, the endopelvic fascia and the anterior vaginal wall) attached to the arcus tendineus fascia and the levator ani muscle. This hammock would allow for correct intra-abdominal position of the bladder neck and proximal urethral. Furthermore he described a sphincteric system, comprised of striated muscle tissue surrounding the bladder neck.

When a compressed urethra fails to close we speak of ISD. In patients with ISD, the urethra and bladder neck can both be hypermobile or not. Stress incontinent women with ISD can be urodynamically characterised by a very low maximum urethral closure pressure (MUCP) < 20cm H^20 and a low Valsavalva leak point pressure (VLPP) <90 cm H^20. However, in treating stress urinary incontinence it is of less importance whether there is urethral hypermobility or ISD.

Decisions on a treatment regimen being either physiotherapy or slingsurgery are not made by this urodynamically distinction.

RISK FACTORS

The most frequently reported risk factors for developing incontinence are: pregnancy, mode of delivery, parity and Body-Mass-Index.[17,18] Furthermore, women who experience incontinence during pregnancy are at risk for developing urinary incontinence later in life.[3,19] More than half of all pregnant women experience some incontinence during pregnancy, which often resolves in the post-partum period.[20] Increasing parity and vaginal delivery increase the risk for stress urinary incontinence in later life. Especially when assisted vaginal birth (vacuum and forcipal extraction) has been performed.[20,21]

TREATMENT FOR STRESS URINARY INCONTINENCE: PELVIC FLOOR MUSCLE TRAINING

In the Netherlands, women presenting with incontinence complaints usually consult their general practitioner (GP) first. The GP Dutch guidelines on stress incontinence advocates to either start treatment with pelvic floor muscle training (physiotherapy) by the GP, or to refer to a specialised physiotherapist.[22] Women are also allowed to contact a pelvic floor muscle physiotherapist by their own initiative. A report by the Health Counsel in 2001 showed that only 1.9% of women presenting with urinary incontinence for the first time were referred to a physiotherapist by their GP.[23] Although this report was written in 2001 we may assume that the majority of incontinent women are treated by the GP. This treatment consists of giving verbal and/or written instructions on how to contract and train the pelvic floor muscles, with a first revision after 3 months. This is clearly different from the weekly or two weekly, 30-minute individual sessions given by a pelvic floor muscles physiotherapist. If treatment by the GP fails, it is currently advocated to start specialised physiotherapy.

Kegel first reported the benefits of pelvic floor muscle training for women with stress urinary incontinence in 1948.[24] The rationale for physiotherapy is not completely understood but it is thought that increased muscle volume and stiffness add support to the bladder/urethra.[25,26]

In physiotherapy, women are educated about the function of the pelvic-floor muscles, bladder function, and how to perform a correct pelvic-floor muscle contraction. Training includes both maximal and submaximal pelvic floor contractions. In addition, stress incontinent women are taught the so-called " Knack", a short muscle contraction prior to an intra-abdominal pressure rise such as sneezing.[27] According to the 2014 Cochrane review on physiotherapy[28], this treatment is statistically significant more likely to improve incontinence symptoms when compared with no or sham treatment. The Cochrane describes that comparing the different studies on effectiveness of physiotherapy is difficult because of heterogeneity. Furthermore there is a wide variability in physiotherapy programs and there still is uncertainty about the best physiotherapy treatment regimen.[26,28,29]

In the Netherlands, specialised physiotherapists administer physiotherapy. Approximately 65% of women treated with physiotherapy experience improvement of their complaints. However, a 100% cure rate is only recorded in 15% to 20% of women. The long-term efficacy of physiotherapy is debatable. When conservative measures fail or the treatment effect is unsatisfactory, women may proceed to slingsurgery.

SURGICAL TREATMENT FOR STRESS URINARY INCONTINENCE

Until the late 20th century abdominal urethropexy following the method of Burch or Marchall-Marchetti-Kranz (**Figure 2**) was the gold standard in stress incontinence surgery. Surgery for stress urinary incontinence made an immense progression with the introduction of the minimally invasive midurethral synthetic slingsurgery in 1996 by Ulmsten.[30]

In midurethral slingsurgery, a small vaginal incision is made under the urethra through which a macroporous polypropylene tape of approximately 1 cm in width is placed tension free sub-urethrally using an inside (vagina) out (abdominal wall) retropubic route. When intra-abdominal

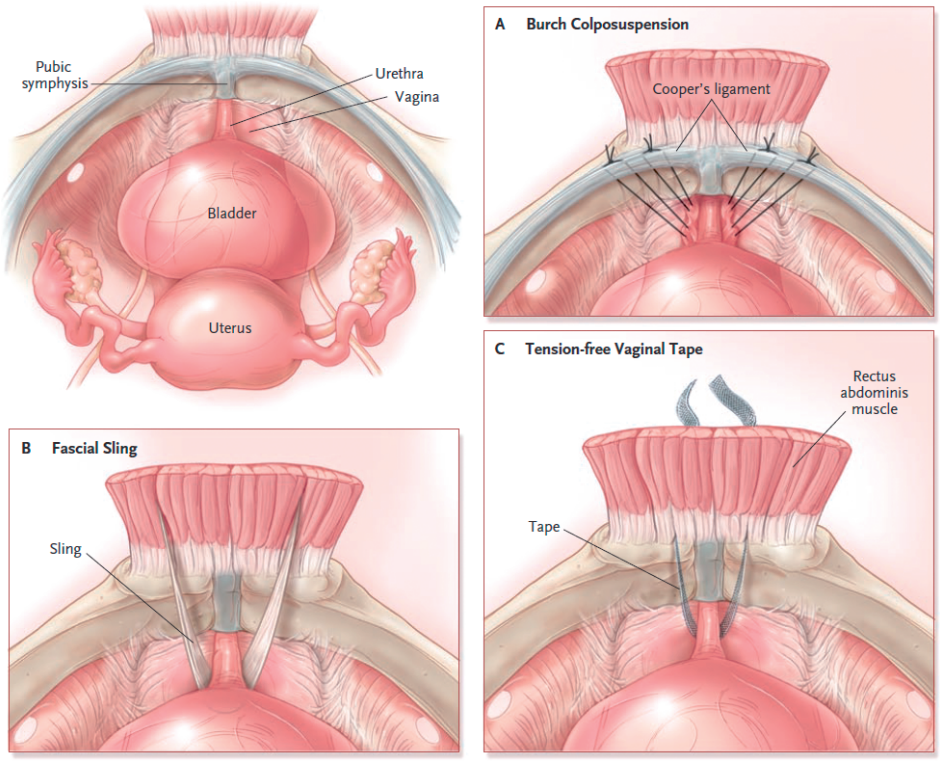


Figure 2: Surgical Procedures for Treating Stress Incontinence. From: Rebecca Rogers : Urinary Stress Incontinence in Women[36]

pressure increases, the urethra will be compressed to the sling and continence will be restored. In a state of physical rest the sling will lie loosely under the urethra, ensuring the possibility of normal non-obstructive micturion. Minimal intra- and postoperative complications were one of the big advantages presented in the first report on the midurethral synthetic sling procedure. High cure rates were found and operation time was shorter than in the classic laparotomic Burch operation.

To minimise the risk of complications (bladder perforation), the procedure of partially blind passage of the tape retro-pubically altered. Delorme developed a new outside-in transobturator route for insertion of the tape: the Trans-Obturator Tape (TOT).[31] Although outcomes concerning cure of incontinence complaints were good, the first transobturator tape used was found to have a high tape exposure rate and was withdrawn from the market. In conformity with the material used for the original midurethral sling, (TVT) de Leval introduced the Tension-free Vaginal Tape Obturator (TVT-O).[32] This procedure uses an inside (vagina) out (adductor loge of the upper leg) route trough the obturator foramens. It was found to cause less intra-abdominal complications such as bladder perforations with equally high cure rates.[32]

Midurethral sling placement via the retropubic "classical' or transobturator route using polypropylene tapes are now widely accepted as safe and effective procedures.[33] An advantage of these procedures, as mentioned above is that they can be performed in day-care. After a midurethral sling procedure 50-90% of women are objectively cured (100% dry) and 60-90% of women show subjective improvement.[10,33,34] Furthermore, this effect seems to be longstanding.[35]

Although minimally invasive, slingsurgery does carry a risk of complications. The most common complication is the occurrence of bladder perforation during the surgical procedure (approximately 3-6% for the retropubic and < 1% for the transobturator route) and carries no long-term morbidity when recognised during surgery.[33] Major complications are rare with an incidence of 0.007% for bowel perforation and 0.012% for vascular injury.[37] Adverse outcomes of slingsurgery in terms of the development of new incontinence symptoms may be of bigger concern. Voiding difficulties and symptoms of overactive bladder complaints are reported in 2-23% of cases.[10,38] These symptoms are most likely related to a non-tension free placing of the midurethral sling or hyper-reactivity of the surrounding fibrous tissues.

PATIENT REPORTED OUTCOMES AND HEALTH RELATED QUALITY OF LIFE

Stress urinary incontinence affects health related quality of life (HRQoL) and the implications might vary per individual women. The concept of HRQoL is complex and can be associated with both health related factors (emotional, physical, functional, social and mental well-being) and non-health related factors (work, income, environment and social factors). The effect on HRQoL can be caused by the actual leakage of urine or the fear of leakage. This may cause distress, embarrassment and limitations in everyday functioning. The severity of symptoms is the main predictor of HRQoL outcomes in women with urinary incontinence, the type of incontinence is of lesser importance.[39–41] Furthermore, almost 25% of women with urinary incontinence experience urinary incontinence during sexual intercourse, which could lead to sexual disfunctioning.[42,43]

The severity of incontinence, increasing age and the impact on HRQoL are associated with help seeking behaviour.[4,5] It is remarkable to notice that women with stress urinary incontinence are less likely to consult a doctor for their complaints compared to women with other forms of incontinence. This could be because women with stress urinary incontinence more often experience mild symptoms and are generally younger.[5] Moreover, women experience their incontinence differently. A drop of incontinence can be a severe problem for one woman while it may not bother the other. Furthermore, embarrassment is a factor preventing women from seeking help.[44]the researchers deliberated on them until consensus was reached.\n\nFINDINGS: All women suffered from pelvic floor dysfunction such as urinary incontinence, pelvic floor pain, prolapse, haemorrhoids, anal fissure, constipation and dyspareunia. Midwives and gynaecologists did not prepare them for postpartum pelvic floor problems. The women did not expect the problems to be that severe. They hoped their problems would improve by themselves. The women talked to close initiates (female relatives and friends who had had deliveries themselves

In this thesis HRQoL is defined according to Bowling: "HRQoL is a concept representing individual response to the physical, mental and social effects of illness on daily living which influences the extent to which personal satisfaction with life circumstances can be achieved."[45] In the last decades, clinicians have become more aware that these complaints need treatment and that stress urinary incontinence is not just a physical disorders. This is why measuring Health Related Quality of Life and patient reported outcomes have become more important in research and in counselling for treatment outcomes. Merely measuring objective outcomes provides information to clinicians but is of limited interest to patients, as they often correlate poorly with their functional capacity and actual well-being or patient perceived improvement. Another reason why it is important to measure patient reported outcomes is that two patients with the same complaints often experience and respond differently to these complaints. Moreover, clinicians tend to underestimate improvement of complaints after treatment, especially in the older patient.[46] These considerations explain why patients, clinicians and health care administrators are interested in the concept of patient reported outcomes. This is also taken into account in the Dutch report on the future perspective of hospital care: "Medisch specialistische zorg 20/20" which was published in 2011.[23] This report describes that quality of care should be formulated in functional terms, and not only in cure of complaints. If we want to move towards patient centered care, patient reported outcomes are key in research.

Although many have performed research on treating urinary incontinence and the impact on HRQoL, we found that a literature review on HRQoL and treatment of stress urinary incontinence has not been performed. Most reviews focused mainly on objective outcomes. We present a review of the effect of pelvic floor muscle training and midurethral slingsurgery on Health Related Quality of Life. With this review we aim to compare the effect of physiotherapy and midurethral slingsurgery on HRQoL in stress urinary incontinent women. This comparison should lead to better understanding and awareness of the influence treatment has on HRQoL in women with stress urinary incontinence

THE PHYSIOTHERAPY OR TVT RANDOMISED EFFICACY TRIAL

As mentioned before, both pelvic floor muscle training and midurethral slingsurgery improve stress incontinence complaints and HRQoL. Some might say that slingsurgery is a more effective treatment based on the currently available research. However, slingsurgery carries a risk of peri-operative complications while physiotherapy does not. Physiotherapy, on the other hand, has only been compared to performing sham therapy and seems to be less effective than slingsurgery. That is why we set up the first trial comparing physiotherapy and slingsurgery in a randomised fashion. In this thesis the results of the Physiotherapy OR Tvt Randomised Efficacy Trial (PORTRET study) are reported. The inclusion and randomisation of women with moderate to severe stress urinary incontinence started in March 2008 and ended in May 2010. We are not only interested in comparing clinical outcomes of both treatment options but also aim to predict which women would benefit more from initial slingsurgery or initial physiotherapy.

PATIENT CENTERED CARE

The current advice for all women with stress urinary incontinence is to start with physiotherapy.[28] But, are all women with stress urinary incontinence comparable? We question this advice, as it seems more logical to take more factors e.g. personal preference, expectations and severity of complaints, into consideration when compiling a treatment strategy. Some women could be better off by starting physiotherapy while others would rather directly undergo slingsurgery. Factors reported in previous literature that could negatively influence physiotherapy outcomes are: severity of incontinence, number of incontinence episodes at start of treatment, poor outcome of previous physiotherapy, insufficient adherence to therapy, poor physical health, vaginal delivery, obesity, level of education, and age.[7,20,47–49]

In Chapter 5 we will present a prediction rule for the chance of slingsurgery after initial physiotherapy. With the outcomes of this model we aim to provide an evidence-based background to counsel for the optimal initial treatment strategy. By providing women with the chance of slingsurgery after physiotherapy, personal preference and expectations of the patient can be taken in account.

COST-EFFECTIVENESS

Besides the importance of identifying the correct treatment strategy for the individual woman, health economic evaluations can guide policy makers in optimising treatment approach. This guidance should be based on scientific information. In 2011 the cost for urinary incontinence materials were estimated at € 148 million. For stress incontinence the costs for physiotherapy were estimated to be € 4 million per year and specialised hospital treatment costs were estimated at € 84 million by the "college voor zorgverzekeringen" (CVZ).[50] With an ageing population in the Netherlands it is expected that cost for all types of incontinence will increase

in the future. Therefore it is important to evaluate costs of individualised treatment for stress urinary incontinence. Only with the support of health policy makers, the implementation of changing the initial treatment approach can be achieved. In order to acquire their support a scientific evaluation of these costs is needed.

A direct comparison between initial physiotherapy and initial slingsurgery taking the cost aspect into account has not been performed. The aim of reports on cost-effectiveness analysis is not to save money, but to use the available health care budget in such a manner that as much health can be provided for the population. This is called health maximisation.[51] A cost-effectiveness analysis should be used as guidance for health care policy makers and clinicians. In this thesis, we present a cost analysis for the treatment of stress urinary incontinence to guide us in personalised care.

By combining the subjective and objective outcomes of treatment for stress urinary incontinence with a patient selection tool and a cost-effectiveness analysis, this thesis aims to provide a scientific basis for individualised care for female urinary stress incontinence.

OUTLINE OF THIS THESIS

Chapter 2 describes a systematic review on the literature regarding effects on health related quality of life of pelvic floor muscle training and midurethral slingsurgery. We conducted a systematic literature search and appraised all articles on participant entry criteria, study design, intervention, questionnaire, objective cure, and HRQoL questionnaires.

Chapter 3 presents the protocol of the Physiotherapy OR Tvt Randomised Efficacy Trial (PORTRET study). A multi-centre randomised controlled trial was performed for women between 35 - 80 years old with moderate to severe, predominantly stress urinary incontinence. Women were assigned to either physiotherapy or midurethral slingsurgery.

In **Chapter 4** we compare pelvic floor muscle training with midurethral slingsurgery on objective and subjective outcomes in the form of the prospective randomised trial described in Chapter 3. The outcomes at 12 months follow-up are presented. Crossover between groups was allowed. The primary outcome was subjective improvement, measured by means of the Patient Global Impression of Improvement at 12 months.

In **Chapter 5** we constructed a prediction model for crossover to midurethral slingsurgery. This analysis was performed with prospectively acquired data from women in the initial pelvic floor muscle training arm of the PORTRET study. This is a cohort study including women who were allocated to the initial physiotherapy arm from the PORTRET study.

Chapter 6 presents the cost-effectiveness analysis of initial pelvic floor muscle training versus initial midurethral slingsurgery. Data are analysed following the intention to treat principle. Treatment costs are collected using questionnaires and generic quality of life is measured with the EuroQol 5D questionnaire to calculate the incremental cost per quality adjusted life year.

Chapter 7 and **8** discuss and summarise the results and conclusions.

REFERENCES

1. Gil KM, Somerville AM, Cichowski S, et al. Distress and quality of life characteristics associated with seeking surgical treatment for stress urinary incontinence. Health Qual Life Outcomes. 2009; 7:8.
2. Labrie J, Fischer K, Vaart CH van der. Health-related quality of life. The effect of pelvic floor muscle training and midurethral sling surgery: a systematic review. Int Urogynecol J Pelvic Floor Dysfunct. 2012; 23(9):1155-62.
3. Milsom I, Lapitan M, Nelson R, et al. Epidemiology of Urinary (UI) and Faecal (FI) Incontinence and Pelvic Organ Prolapse (POP). In: Abrams, PLC, Saad, K. Wein A, ed. Incontinence, 4th International Consultation on Incontinence. 4th ed. Paris: Health publication Ltd.; 2009; 35-113.
4. Shaw C, Das Gupta R, Williams KS, et al. A survey of help-seeking and treatment provision in women with stress urinary incontinence. BJU Int. 2006; 97(4):752-7.
5. Hannestad YS, Rortveit G, Sandvik H, et al. A community-based epidemiological survey of female urinary incontinence: the Norwegian EPINCONT study. Epidemiology of Incontinence in the County of Nord-Trøndelag. J Clin Epidemiol. 2000; 53(11):1150-7.
6. Imamura M, Abrams P, Bain C, et al. of the effectiveness and cost-effectiveness stress urinary incontinence. Health Technol Assess (Rockv). 2010; 14(40).
7. Cammu H, Van Nylen M, Blockeel C, et al. Who will benefit from pelvic floor muscle training for stress urinary incontinence? Am J Obstet Gynecol. 2004; 191(4):1152-7.
8. Lamers BHC, van der Vaart CH. Medium-term efficacy of pelvic floor muscle training for female urinary incontinence in daily practice. Int Urogynecol J Pelvic Floor Dysfunct. 2007; 18(3):301-7.
9. Bø K, Kvarstein B, Nygaard I. Lower urinary tract symptoms and pelvic floor muscle exercise adherence after 15 years. Obstet Gynecol. 2005; 105(5 Pt 1):999-1005.
10. Novara G, Artibani W, Barber MD, et al. Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence. Eur Urol. 2010; 58(2):218-38.
11. Ogah J, Cody J, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane database Syst Rev. 2010; (1):CD006375.
12. Latthe PM, Foon R, Toozs-Hobson P. Transobturator and retropubic tape procedures in stress urinary incontinence: a systematic review and meta-analysis of effectiveness and complications. BJOG. 2007; 114(5):522-31.
13. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/ International Continence Society (ICS) Joint Report on the Terminology for Female Pelvic Floor Dysfunction. Neurourol Urodyn. 2010; 20:4-20.
14. Sandvik H, Hunskaar S, Seim A, et al. Validation of incontinence severity index in female urinary implementation in an epidemiological survey. Management. 1993; 497-499.
15. Enhörning G. Simultaneous recording of intravesical and intra-urethral pressure: a study on urethral closure in normal and stress incontinent women. Acta Chir Scand. 1961; suppl(276):1-68.
16. DeLancey JOL. Structural support of the urethra as it relates to stress urinary incontinence: the hammock hypothesis. Am J Obstet Gynecol. 1994; 170(6):1713-1723.
17. Waetjen LE, Liao S, Johnson WO, et al. Factors associated with prevalent and incident urinary incontinence in a cohort of midlife women: a longitudinal analysis of data: study of women's health across the nation. Am J Epidemiol. 2007; 165(3):309-18.
18. Danforth KN, Townsend MK, Lifford K, et al. Grodstein F. Risk factors for urinary incontinence among middle-aged women. Am J Obstet Gynecol. 2006; 194(2):339-45.
19. Viktrup L, Rortveit G, Lose G. Risk of stress urinary incontinence twelve years after the first pregnancy and delivery. Obstet Gynecol. 2006; 108(2):248-54.
20. Burgio K, Goode PS, Locher JL, et al. Predictors of outcome in the behavioral treatment of urinary incontinence in women. Obstet Gynecol. 2003; 102(5):940-947.
21. Handa VL, Blomquist JL, McDermott KC, et al. Pelvic floor disorders after vaginal birth: effect of episiotomy, perineal laceration, and operative birth. Obstet Gynecol. 2012; 119(2 Pt 1):233-9.
22. Lagro-Janssen A, Breedveldt Boer H, van Dongen J, et al. NHG-Standaard Incontinentie voor Urine. NHG-Standaarden voor huisarts. 2009; 792-806.
23. Meijerink M, Blerck-Woerdman A, Bosma H, et al. Medisch-Specialistische Zorg in 20/20. 2011.
24. Kegel A. Progressive resistance exercise in the functional restoration of the perineal muscles. Am J Obstet Gynecol. 1948; 56:238-249.
25. Bø K. Pelvic floor muscle training is effective in treatment of female stress urinary incontinence, but how does it work? Int Urogynecol J Pelvic Floor Dysfunct. 2004; 15(2):76-84.

26. Dumoulin C. Determining the optimal pelvic floor muscle training regimen for women with stress urinary incontinence. Neurourol Urodyn. 2011; 753(June):746-753. doi:10.1002/nau.
27. Miller J, Ashton-Miller J, DeLancey J. A pelvic muscle precontraction can reduce cough-related urine loss in selected women with mild SUI. J Am Geriatr Soc. 1998; 46:870-874.
28. Dumoulin C, Hay-Smith J. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev. 2014;(5).
29. Castro RA, Arruda RM, Zanetti MRD, et al. Single-Blind randomized, controlled trial of pelvic floor muscle training, electrical stimulation, vaginal cones, and no active treatment in the management of stress urinary incontinence. Biostatistics. 2008; 465-472.
30. Ulmsten U, Henriksson L, Johnson P, el al. An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 1996; 7(2):81-86.
31. Delorme E, Droupy S, de Tayrac R, et al. Transobturator tape (Uratape). A new minimally invasive method in the treatment of urinary incontinence in women. Prog Urol. 2003; 13(4):656-9.
32. De Leval J. Novel Surgical Technique for the Treatment of Female Stress Urinary Incontinence: Transobturator Vaginal Tape Inside-Out. Eur Urol. 2003; 44(6):724-730.
33. Ogah J, Cody D, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women: a short version Cochrane review. Neurourol Urodyn 2011; 291:284-291. doi:10.1002/nau.
34. Latthe PM, Singh P, Foon R, et al. Two routes of transobturator tape procedures in stress urinary incontinence: a meta-analysis with direct and indirect comparison of randomized trials. BJU Int. 2010; 106(1):68-76.
35. Nilsson CG, Palva K, Aarnio R, Morcos E, Falconer C. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2013; 24(8):1265-9.
36. Rogers R. Urinary stress incontinence in women. N Engl J Med. 2008; 1029-1036.
37. Atherton MJ, Stanton SL. The tension-free tape reviewed: an evidence-based review from inception to current status. Br J Obs Gynaecol 2005. 2005; 112:534-546.
38. Latthe PM, Foon R, Toozs-Hobson P. Transobturator and retropubic tape procedures in stress urinary incontinence: a systematic review and meta-analysis of effectiveness and complications. BJOG. 2007; 114(5):522-31.
39. Monz B, Chartier-Kastler E, Hampel C. Patient characteristics associated with quality of life in European women seeking treatment for urinary incontinence: results from PURE. Eur Urol. 2007; 51(4):1073-81; discussion 1081-2. d
40. Van der Vaart CH, de Leeuw JRJ, Roovers JPWR, et al. The effect of urinary incontinence and overactive bladder symptoms on quality of life in young women. BJU Int. 2002; 544-549.
41. Samuelsson E, Victor A, Tibblin G. A population study of urinary incontinence and nocturia among women aged 20-59. Prevalence, well-being and wish for treatment. Acta Obstet Gynecol Scand. 1997; 76(1):74-80.
42. Koch LH. Help-seeking behaviors of women with urinary incontinence: an integrative literature review. J Midwifery Womens Health. 2006; 51(6):e39-44.
43. Hilton P. Urinary incontinence during sexual intercourse: a common, but rarely volunteered, symptom. Br J Obstet Gynaecol. 1988; 95(4):377-81.
44. Buurman MBR, Lagro-Janssen ALM. Women's perception of postpartum pelvic floor dysfunction and their help-seeking behaviour: a qualitative interview study. Scand J Caring Sci. 2013; 27(2):406-13.
45. Bowling A. Health care research: measuring health status. Nurs Times. 1992; 88(31):31-4.
46. Tannenbaum C, Brouillette J, Corcos J. Rating improvements in urinary incontinence: do patients and their physicians agree? Age Ageing. 2008; 37(4):379-83.
47. Hendriks EJM, Kessels AGH, Vet HCW De, et al. Prognostic Indicators of Poor Short-Term Outcome of Physiotherapy Intervention in Women With Stress Urinary Incontinence. Neurourol Urodyn. 2010; 343:336-343.
48. Truijen G, Wyndaele JJ, Weyler J. Conservative Treatment of Stress Urinary Incontinence in Women: Who will Benefit? Int Urogynecol J Pelvic Floor Dysfunct. 2001;12(6):386-390.
49. Theofrastous JP, Wyman JF, Bump RC, et al. Effects of pelvic floor muscle training on strength and predictors of response in the treatment of urinary incontinence. Neurourol Urodyn. 2002; 21(5):486-90.
50. www.cvz.nl.
51. Weinstein M, WB S. Foundations of cost-effectiveness analysis for health and medical practices. N Engl J Med. 1977; 296:716-721.


2

HEALTH RELATED QUALITY OF LIFE. THE EFFECT OF PELVIC FLOOR MUSCLE TRAINING AND MIDURETHRAL SLING SURGERY: A SYSTEMATIC REVIEW

J. Labrie, K. Fischer and C.H. van der Vaart

Int Urogynecol J. 2012 Sep;23(9):1155-62

ABSTRACT

Stress urinary incontinence (SUI) is a bothersome condition affecting health-related quality of life (HRQoL) to a great extent in women. From a patient's perspective, improving HRQoL is probably equally important as objective cure of SUI. Our objective was to assess the effect of pelvic floor muscle training (physiotherapy) and midurethral slingsurgery on condition-specific HRQoL in women with SUI. A systematic literature search was conducted in the PubMed, Embase, and Cochrane databases. Studies reporting on HRQoL after intervention for SUI or mixed incontinence with a predominant SUI component were selected. Retrieved articles were appraised by all authors regarding; participant entry criteria, study design, intervention, questionnaire, objective cure, and HRQoL presentation. There were three articles reporting HRQoL after physiotherapy and 11 after midurethral slingsurgery. Improvement in HRQoL seemed higher after midurethral slingsurgery compared with physiotherapy. However, methods of HRQoL assessment varied widely, limiting the possibility of comparison and interpretation between studies.

INTRODUCTION

Stress urinary incontinence (SUI) is defined by the International Continence Society (ICS) as involuntary loss of urine on effort, physical exertion, or sneezing or coughing.[1] It is estimated that up to 30 % of the female adult population in Western countries experience some form of SUI.[2,3] SUI is a major disabling public health problem, with considerable negative effects on health-related quality of life (HRQoL), making this a major driving factor for women with SUI to seek treatment.[4]

There are two treatment options that aim to either reduce or, where possible, cure SUI. Primary treatment is pelvic floor muscle training (physiotherapy) by certified physiotherapists. If this treatment fails or falls short, midurethral synthetic slingsurgery, either by a retropubic or transobturator route, is the next option. Although the physician's primary goal may be to completely cure incontinence, improvement in HRQoL may be of equally or more importance from the patient's perspective. Consequently, as stated by Black and Downs in their 1996 review on the effectiveness of surgery for SUI, patient-reported outcomes such as HRQoL should be included in research.[5]

HRQoL is usually measured with so-called condition- or disease-specific questionnaires that focus on aspects of health that are specifically related to the disease under study and include physical, functional, social, and emotional factors of well-being. Until now, reviews on the efficacy of therapy for SUI have mainly focussed on subjective and/or objective cure. A systematic review on the effect of physiotherapy and slingsurgery on condition-specific HRQoL has not been performed to date.

This review aimed to address the following question: What is the effect of physiotherapy and midurethral slingsurgery on condition-specific HRQoL after 6–12 months of follow-up in stress urinary incontinent women?

MATERIALS AND METHODS

This review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[6] Methods of analyses and inclusion criteria were not documented in a protocol. A systematic literature search was conducted in PubMed, Embase, and Cochrane databases (**Table 1**). Limits were used for language (English, Dutch, German), and for publication date (January 1990 to December 2009). To ensure a broad search of the literature, search terms for possible interventions were not included. Abstracts and meeting or convention reports were excluded. Duplicate articles were removed using Ref-Works, online reference software.

All articles were screened on title and abstract. Studies reporting on HRQoL after treatment for SUI or mixed incontinence with a predominant SUI component were selected. Treatment included physiotherapy with or without biofeedback, electromagnetic stimulation, or electrical stimulation or midurethral slingsurgery (retropubic or transobturator approach). Studies were assessed by the principal author (JL). Articles were excluded when volunteers were included (studies in which participants were recruited from the general population on a voluntary basis, i.e., not actively help seeking women), if the articles reported on urge incontinence or mixed incontinence with predominant urge component, if previous anti-incontinence surgery was performed in >10 %

of participants, if concomitant prolapse needing surgery/or concomitant prolapse repair was performed, or if a validated HRQoL questionnaire was used that received a grade recommendation lower than grade A from the International Consultation on Incontinence (ICI).[7] The remaining articles were critically appraised by all authors using the following criteria: at least 50 patients in the study, a validated questionnaire was used, a minimum of 6 months follow-up, pre- and postoperative HRQoL scores or differences in scores after treatment were presented, and adequate methods described. Articles were scored on adequate description of inclusion and exclusion criteria, appropriate design, baseline characteristics, and the type of intervention. When the reviewers disagreed on inclusion or exclusion of an article for reviewing, this was resolved by discussion.

Table 1. Systematic search strategy

DOMAIN	AND	*OUTCOME*
("Urinary Incontinence" OR "Urinary Stress Incontinence" OR "Stress Urinary Incontinence" OR "SUI" OR "USI" OR "urine loss")		*("quality of life" OR "QoL" OR "QALY" OR "efficacy" OR "effectiveness")*

PubMed (1671)	*EMBASE (1319)*	*Cochrane (817)*
- Index search - Title / Abstract - Language limits - 1990-2009 www.pubmed.com	- Explosion search - Articles with abstracts - Embase only - Language limits - 1990-2009 www.embase.com	- Title / Abstract / Keywords - All of the Cochrane Library - Language limits - 1990-2009 www.thecochranelibrary.com

After critical appraisal, data on subjective and objective cure of incontinence were collected using the definitions used in the articles. Five different condition-specific HRQoL questionnaires were used in the selected studies. The Incontinence Impact Questionnaire (short-form) IIQ(-7)[8,9], Kings Health Questionnaire (KHQ)[10], Incontinence Quality of Life Questionnaire (I-QoL)[11,12], International Consultation on Incontinence Questionnaire Short Form (ICIQ-UI SF)[13], and Bristol Female Lower Urinary Tract Symptoms Questionnaire (BFLUTS)[14]. All of these questionnaires received the highest recommendation (grade A) from the 4th International Consultation on Incontinence, Paris 5–8 July 2008[7].

To enable comparison, HRQoL scores assessed with different questionnaires were normalised to a scale ranging from 0–100. A score of 100 on this scale represents the lowest possible HRQoL, and a score of zero implicates perfect HRQoL score, representing a patient without any incontinence-related complaints. For the KHQ, we chose to use the Incontinence Impact domain to allow for a better comparison to be made with other questionnaires. **Table 2** presents the main characteristics of the questionnaires used in our review.

The IIQ-7, I-QoL, and KHQ produce scores that range from 0 to 100 and therefore do not require normalisation. However, in three articles, a questionnaire was used that produced scores that needed to be recalculated into a correct scale range.[15–17] When studies compared two midurethral slings, all patients receiving slings were grouped together and a weighted mean of HRQoL for the complete study group was calculated.

Table 2. Condition Specific Health Related Quality of Life Questionnaires

Questionnaire[a]	Specific for	Measuring	Items	Domains	Score range	Used for review
BFLUTS	Female lower urinary tract symptoms.	Symptoms and Impact on sexual function and HRQoL	34	- Symptoms - Sexual function - Quality of life	None[b]	Overall interference with life
ICIQ UI SF	Male/female urinary incontinence	Symptoms and impact on HRQoL	4	- frequency - amount of leakage - overall interference. - perceived cause of incontinence.	0-21	Total score
IIQ IIQ-7	Female urinary incontinence	Impact on HRQoL	30 7	- physical activity - travel - social relationships - emotional health	0-100	Total score
I-Qol	Female urinary incontinence	Impact on HRQoL	22	- avoidance and limiting behaviors - psychosocial impacts - social embarrassment	0-100	Total score
KHQ	Female urinary incontinence	Impact on HRQoL	21	- general health perception, incontinence impact, - role limitations, - physical limitations, - social limitations, - personal relationships, emotions, - sleep/energy, - severity of urinary symptoms.	0-100	Incontinence Impact domain

BFLUTS: Bristol Female Lower Urinary Tract Symptoms Questionnaire, HRQoL: health-related quality of life, ICIQ-UI SF: International Consultation on Incontinence Questionnaire Short Form, IIQ-7: Incontinence Impact Questionnaire short form, I-QoL: Incontinence Quality of Life questionnaire, KHQ: Kings Health Questionnaire
[a] All questionnaires have the highest grade (A) of recommendation by the International Consultation on Incontinence, [b] scores are presented as percentage of women who positively answer questions

RESULTS

Search and selection

A total of 3,807 publications were identified: 1,671 in MEDLINE, 1,319 in Embase, and 817 in Cochrane. After removing duplicates, 1,480 articles remained, titles and abstracts were screened for relevance and applicability, and 1,402 articles were excluded. Randomised controlled trials (RCTs) comparing physiotherapy and midurethral slingsurgery were not identified, and based on our selection criteria, the number of high-quality RCTs proved to be limited; therefore, single-arm observational studies as well as trials comparing different surgical techniques were included.

The remaining 78 articles were screened in full text, which resulted in the exclusion of 59 additional articles: 23 for domain (previous surgery for incontinence >10 %), 15 for inadequate follow-up (< 6 months), 13 for intervention (concomitant prolapse surgery without subgroup

analysis), and eight for outcome (no presentation of quality of life or lower than grade A recommended questionnaire as defined by the ICI was used). The remaining 19 publications were critically appraised (by two independent reviewers JL and KF), after which an additional four studies were excluded because of low number of patients (< 50). Eventually, 15 articles were selected: 12 reported on midurethral tapes[15–26] and three on physiotherapy.[27–29] There were 11 RCTs (two addressing physiotherapy and nine addressing slingsurgery) and four cohort studies (three addressing slingsurgery and one physiotherapy). Cross-referencing and a related-article search was performed for the 15 articles, but no additional literature was identified. The study selection process is displayed in **Figure 1. Table 3** summarises the main results of critical appraisal. Two studies reported adequate blinding, and all included RCTs used adequate randomisation.

In four of the 15 studies, 6 months of follow-up was performed, and 12 months of follow-up was assessed in ten; one study reported data on 24 months of follow-up. Loss to follow-up varied greatly between studies, from 0 % to 57.2 %, with higher loss to follow-up rates in the physiotherapy studies

Study population

Patient numbers per study varied from 59 to 634, with 2,594 surgical patients versus 373 patients who underwent physiotherapy included in this review, all of whom were diagnosed with SUI or mixed incontinence with a predominant SUI component. In all studies, SUI was assessed with urodynamics, with the exception of one physiotherapy study[29] and three surgical studies[17,22,26] in which clinical evaluation of SUI with or without urodynamic study was performed. There were some considerations to take into account with regard to study population. One surgical study[24] included patients with concomitant prolapse, but results from patients without concomitant prolapse were presented separately, which permitted this study to be included in our review. One physiotherapy study[29] reported previous vaginal surgery in 11 % of patients; however, incontinence-related surgery was performed in <10 % of women (data provided by authors), and that study, therefore, was also included. Only one surgical study[15] excluded patients who underwent previous physiotherapy. It is unclear in the other surgical studies whether patients had a history of physiotherapy

Objective cure

Although most studies used a negative stress test to objectively measure cure, definitions of testing varied widely (**Table 3**). Even with varying definitions, objective cure rate among surgical studies was comparable (78.9– 94.3 %). Only one physiotherapy study reported a cure rate, which was considerably lower than in the surgical studies. (33 %).[29]

Intervention

Diversity in conservative treatment protocols is a problem when reviewing the effect of physiotherapy for SUI. Whereas all patients from the RCT by Gilling et al.[28] were given low-intensity physiotherapy with or without electromagnetic stimulation, patients from the study by Neumann et al..[29] were treated according to clinical practice without study treatment protocol. Conversely, in the study by Bø et al..[27], patients in the intervention group were

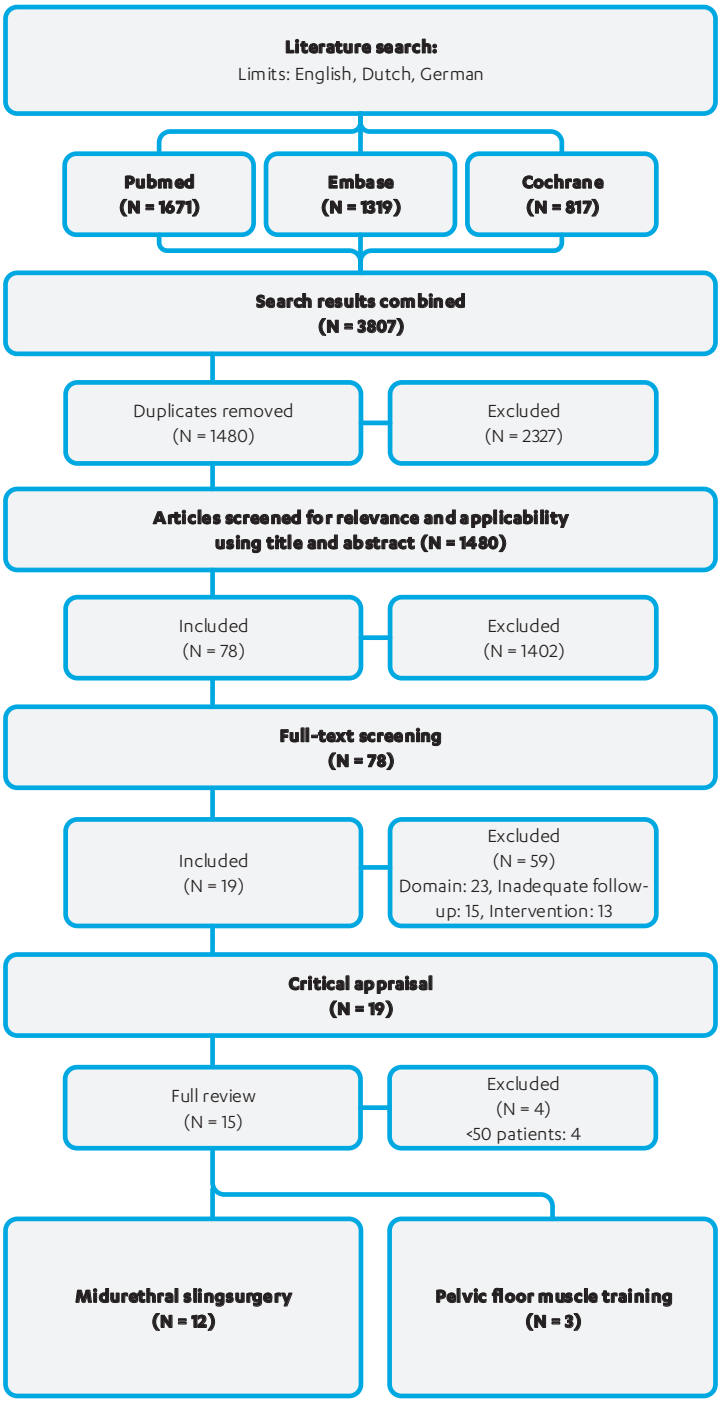


Figure 1. Identification of studies reporting on Health Related Quality of Life after treatment for stress urinary incontinence

given high-intensity physiotherapy as prescribed by study protocol. Surgical studies all used midurethral tape procedures via the retropubic or transobturator route. Outcomes of these procedures are well established, and the similar success rates suggest that treatment aspects of these procedures are comparable. [30,31]

HRQoL

All included studies used questionnaires that were recommended with the highest grade (A) recommendation by the ICI.[7] HRQoL domain scores were presented in only five of the 15 included studies. All studies reported an overall HRQoL score. Comparison of domain HRQoL scores was, therefore, not possible, and only the overall HRQoL scores were used for comparison. Baseline HRQoL scores between studies (after normalisation) differed considerably. Although all studies presented significant improvement in HRQoL after intervention, this improvement appeared to be higher in surgical studies than in physiotherapy studies. Further comparisons were made according to the five different questionnaires used to assess HRQoL across included studies.

IIQ-7

Seven surgical[16–18,21,22,24,26] studies but no physiotherapy study used the IIQ-7 for measuring QoL. All studies presented significant improvement in HRQoL, and overall improvement in HRQoL after slingsurgery was comparable between studies. Baseline scores varied from 33 to 76 points, with improvement ranging from −30 to −49 for all studies using the IIQ-7.

KHQ

The KHQ was used in one surgical[23] and one physiotherapy study.[29] At baseline, symptom severity, expressed as KHQ scores for incontinence impact, was comparable. However, improvement in KHQ score was more pronounced after slingsurgery compared with physiotherapy (−61.7 vs −34 points), but both studies reported significant improvement in HRQoL scores. The one physiotherapy study[28] that also used the KHQ only presented an overall HRQoL score, which could not be compared with the others using the KHQ.

I-QoL

Two studies, one surgical[15] and one physiotherapy, reported HRQoL using the I-Qol questionnaire. Baseline I-Qol scores varied widely between studies, indicating that the impact of incontinence severity on HRQoL was not comparable between different study groups. Both studies, however, reported a statistically significant improvement after treatment. The effect of slingsurgery thus appeared to be higher than the effect of physiotherapy.

ICIQ-UI SF

The ICIQ-UI SF was used by two surgical studies.[19,20] Scores at baseline were comparable, and both studies presented significant improvement, with some differences in mean change between the two.

Table 3. Critical Appraisal of Studies

#	Author	N=	Design	Inclusion Criteria	Intervention	Question-naire	Age	Follow-up months	Drop-out (%)	Objective cure at follow-up (%)
Midurethral Sling Surgery Studies										
1	Araco et al.	240	RCT	+	RPT vs. TOT	I-QoL	54	12	13	91.8[e]
2	Bakas et al.	98	Cohort	+	RPT	IIQ-7	56	12	0	87.6[d]
3	Krofta et al.	300	RCT	+	RPT vs. TOT	ICI-Q SF	57	12	7.9	89.2[d and e]
4	Meschia et al.	231	RCT	+	RPT vs. TOT	ICI-Q SF	57	6	5.6	90.4[e]
5	Porena et al.	148	RCT	+	RPT vs. TOT	IIQ-7	61	12	2	89.7[e or f]
6	Rinne et al.	267	RCT	+	RPT vs. TOT	IIQ-7	54	12	1.1	94.3[d and e]
7	Ross et al.	182	RCT[a]	+	RPT vs. TOT	IIQ-7	51	12	8.5	78.9 [d]
8	Tomoe et al.	161	Cohort	+	RPT	IIQ-7	58	24	57.2	88.0 [d and e]
9	Schraffordt et al.	634	Cohort	+	RPT	IIQ-7	-	24	4.1	97.0[e]
10	Valpas et al.	70/121[b]	RCT	±	RPT vs. colposuspention	KHQ	49	12	11.4	85.7[e]
11	Wang et al.	88/140[c]	RCT[a]	±	RPT vs. TOT	IIQ-7	59	12	0	94.3[d or e]
12	Ward et al.	175/344[b]	RCT	+	RPT vs. colposuspension	BFLUTS	50	6	9.1	81.0[d or e]
Physiotherapy Studies										
13	Bø et al.	29/30[g]	RCT	±	physiotherapy vs. control	BFLUTS	51	6	6.9	-
14	Gilling et al.	70	RCT[a]	+	physiotherapy + elec. stim. vs. physiotherapy + placebo	I-QoL KHQ	54	6	2.4	-
15	Neumann et al.	274	Cohort	±	physiotherapy	KHQ	47	12	42	33.0[e or f]

BFLUTS: Bristol Female Lower Urinary Tract Symptoms Questionnaire, ICI-Q-SF: International Consultation on Incontinence Questionnaire Short Form, IIQ-7: Incontinence Impact Questionnaire short form, I-QoL: Incontinence Quality of Life questionnaire, KHQ: Kings Health Questionnaire, nr not reported, physiotherapy : pelvic floor muscle training, RCT: randomised controlled trial,
RPT: Retropubic tape, TOT: Trans Obturator Tape
+ inclusion criteria well described with mentioning of concomitant and/or previous surgery, type of incontinence, and concomitant prolapse,
± inclusion criteria described but lacking description of concomitant and/or previous surgery, type of incontinence, or concomitant prolapse.
[a] Blinded studies, [b] patients in retropubic tape group, [c] patients without concomitant prolapse, [d] objective cure defined by 1 h, 24 h or 48 hr. padtest, [e] objective cure defined by negative stress test, [f] objective cure defined by patient reported wet episodes (diary), [g] patients in physiotherapy group

BFLUTS

One surgical[25] and one physiotherapy[27] study used the BFLUTS as a measure of HRQoL. Baseline impact on HRQoL was higher in the surgical study than in the physiotherapy study. The positive

treatment effect appeared to be larger in the surgical study than in the physiotherapy study; however, improvement was significant for both studies.

DISCUSSION

This review aimed to assess the effect of physiotherapy and/or midurethral slingsurgery in improving HRQoL in SUI patients. The method of HRQoL assessment varied widely amongst studies, thus limiting the possibilities of comparison, interpretation, and meta-analyses. However, within these limitations, both treatment options significantly improved HRQoL. Moreover, data from our review suggest that surgical management improves HRQoL to a greater extent than does physiotherapy.

Some studies used generic questionnaires designed to assess HRQoL in a broad population with different diseases to evaluate treatment for incontinence. However, in order to raise the reliability of our study, we chose to focus only on condition-specific HRQoL instruments. These instruments are more sensitive to change after treatment for a specific condition.[32] A number of these condition-specific QoL questionnaires have been developed and adopted by the ICI to assess physical, functional, social, and emotional factors of well-being.

Several challenges were encountered while writing this review. Although the focus of the literature search was on condition-specific HRQoL after intervention for SUI, the selected studies were heterogeneous and the quality of data reporting moderate, with wide variation between studies. The limitations are summarised below.

First, variation across studies in HRQoL scores at both baseline and after treatment was large. In general, patients with lowest HRQoL scores were most likely to improve with treatment. This could be explained either by treatment effect, or it could be due to regression toward the mean: when scores at baseline are more extreme (i.e., further from the mean), they tend to be closer to the mean on the second measurement due to chance.[33]

Second, direct comparison of HRQoL scores from studies in our review was restricted by the use of different condition-specific questionnaires measuring different aspects of HRQoL. We needed to normalise scores to a 0–100 range for all questionnaires to enable HRQoL score comparison. In addition, score recalculation was performed in three studies using inadequate scoring procedures[15–17] (**Table 4**). The scores presented in our review must be viewed in this perspective, and bias may have occurred.

Next to score recalculation, when interpreting HRQoL data, using total scores can lead to misinterpretations and/or loss of information. As questionnaires are composed of several domains, using total scores may obscure important changes in specific domains of interest. For instance, improved physical functioning may be obscured if deterioration occurs on one of the other HRQoL domains. A problem in reviewing the effect of physiotherapy on HRQoL is the wide diversity of physiotherapy protocols used in studies. Three eligible physiotherapy studies were found, each of which used different protocols for treating SUI (i.e., clinical practice; training programs, intensity, or duration). Another problem regarding physiotherapy is the high loss to follow-up in most studies, which could lead to overpresentation of success.

High loss to follow-up could be inherent to physiotherapy studies, as adherence to therapy is an important determinant of success. Amongst patients in whom physiotherapy fails, surgical treatment may be undertaken, and patients could be less motivated to return for follow-up.

Table 4. Pre- and Postoperative Health Related Quality of Life

Author	Baseline	6mnths	12mnths	ΔHRQoL
IIQ-7				
Bakas et al.	49	-	0	-49
Porena et al.	38[a,b]	-	0	-38
Rinne et al.	76[b]	-	33	-43
Ross et al.	33[a]	-	-	-30
Schraffordt et al.	58	12	11	-47
Wang et al.	43	-	9	-34
Tomoe et al.	45	-	3	-42
KHQ Incontinence impact domain part 1				
Valpas et al.	73[a]	-	12	-61
Neumann et al.[c]	67[b]	-	33	-34
I-QOL				
Gilling et al.[c]	37[b]	29	-	-8
Araco et al.	77[b]	-	17	-60
ICI-Q SF				
Krofta et al.	64	-	16	-48
Meschia et al.	74	13	-	-61
BFLUTS-interfering with life overall				
Bo et al.[c]	61,9%	56,0%	-	-5.9%
Ward et al.	98%	30%	-	-68%

Values are expressed as means unless stated differently
BFLUTS denotes Bristol Female Lower Urinary Tract Symptoms Questionnaire; HRQoL denotes Health Related Quality of Life; ICI-Q SF denotes International Consultation on Incontinence Questionnaire Short Form; IIQ-7 denotes Incontinence Impact Questionnaire short form; I-QoL denotes Incontinence-Quality of Life questionnaire; KHQ denotes Kings Health Questionnaire
[a] medians; [b] recalculation to correct score range, [c] pelvic floor muscle training studies

Although several recent reviews focussed on SUI treatment outcome, they focussed primarily on improvement of objective and subjective symptoms. The issue of HRQoL improvement is addressed in the review by Novara et al.[34] and the Cochrane reviews on physiotherapy and minimally invasive synthetic midurethral sling operations for SUI in women[35,36] Consistent with our findings, they stated that different questionnaires for measuring HRQoL were used, making comparisons impossible. However, a significant improvement after SUI treatment was reported. These reviews similarly reported a lack of standardisation of continence status assessment and success rates, making comparison difficult and inaccurate.

Within the restrictions brought on by the limited quality and heterogeneity of studies, this review indicates that improvement in HRQoL is higher after midurethral slingsurgery than physiotherapy. However, both physiotherapy and midurethral slingsurgery improve HRQoL significantly, but with the current available data, direct comparison it is not possible. Only a RCT comparing these interventions following the international standards and using validated questionnaires would make such a comparison possible and could identify the intervention with the best effect on HRQoL.[37]

Although Black and Downs[5] advocated the use of patient-reported outcomes in 1996 to report improvement after SUI therapy, we are still miles away from achieving this goal. Diversity in outcome measures is still large, and only the use of a limited number of internationally accepted tools can change this. Due to the diversity in questionnaires used in studies assessing the effects of therapy on incontinence, studies require large numbers of patients in order to draw concrete conclusions. For instance, when five different questionnaires are used throughout different studies, more patients are needed to evaluate and implement new interventions (e.g. mini slings). Standardised studies will allow early data pooling for meta-analyses, limiting the number of study participants needed to answer the research question.

REFERENCES

1. Haylen BT, de Ridder D, Freeman RM et al. An International Urogynecological Association (IUGA)/ International Continence Society (ICS) Joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn 2010;20:4–20
2. Hannestad YS, Rortveit G, Sandvik H, et al. A community-based epidemiological survey of female urinary incontinence: the Norwegian EPINCONT study. Epidemiology of incontinence in the county of Nord-Trøndelag. J Clin Epidemiol 2000; 53 11:1150–1157
3. Hunskaar S, Lose G, Sykes D, et al. The prevalence of urinary incontinence in women in four European countries. BJU Int 2004; 93(3):324–330
4. Gil KM, Somerville AM, Cichowski S, et al. Distress and quality of life characteristics associated with seeking surgical treatment for stress urinary incontinence. Health Qual Life Outcomes 2009; 7:8
5. Black NA, Downs SH The effectiveness of surgery for stress incontinence in women: a systematic review. Br J Urol 1996; 78 (4):497–510
6. Maher C, Baessler K, Glazener CMA, et al. Surgical management of pelvic organ prolapse in women: a short version Cochrane review. Neurourol Urodyn 2008; 12(3):3–12
7. Staskin DR, Kelleher C, Avery K et al. Patient-reported outcome assessment. In: Abrams P, Cardozo L, Khoury S, Wein A (eds) Incontinence, 4th International Consultation on Incontinence. Health Publication, Paris, 2009; pp 363–412
8. Shumaker SA, Wyman JF, Uebersax JS, et al. Health-related quality of life measures for women with urinary incontinence: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program in Women (CPW) Research Group. Qual Life Res: An Int J Qual Life Aspects Treat, Care Rehabil 1994; 3(5):291–306
9. Uebersax JS, Wyman JF, Shumaker SA, et al. Short forms to assess life quality and symptom distress for urinary incontinence in women: The incontinence
10. impact questionnaire and the urogenital distress inventory. Neurourol Urodyn 2005; 14 (2):131–139
11. Kelleher CJ, Cardozo LD, Khullar V, et al. A new questionnaire to assess the quality of life of urinary incontinent women. Br J Obstet Gynaecol 1997; 104:1374–1379
12. Wagner TH, Patrick DL, Bavendam TG, et al. Quality of life of persons with urinary incontinence: development of a new measure. Urology 1996; 47(1):67–71, discussion 71–2
13. Patrick DL, Martin ML, Bushnell DM, et al. Quality of life of women with urinary incontinence: further development of the incontinence quality of life instrument (I-QOL). Urology 1999; 53(1):71–76
14. Avery K, Donovan J, Peters TJ, et al. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn 2004; 23 (4):322–330
15. Jackson S, Donovan J, Brookes S, et al. The Bristol Female Lower Urinary Tract Symptoms questionnaire: development and psychometric testing. Br J Urol 1996; 77(6):805–812
16. Araco F, Gravante G, Sorge R et al. TVT®-O vs TVT®: a randomized trial in patients with different degrees of urinary stress incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2008; 19(7):917– 926
17. Porena M, Costantini E, Frea B et al. Tension-free vaginal tape versus transobturator tape as surgery for stress urinary incontinence: results of a multicentre randomised trial. Eur Urol 2007; 52 (5):1481–1490
18. Rinne K, Laurikainen E, Kivelä A et al. A randomized trial comparing TVT® with TVT®-O: 12-month results. Int Urogynecol J Pelvic Floor Dysfunct 2008; 19(8):1049–1054
19. Bakas P, Liapis A, Giner M, et al. Quality of life in relation to TVT® procedure for the treatment of stress urinary incontinence. Acta Obstet Gynecol Scand 2006; 85(6):748–752
20. Krofta L, Feyereisl J, Otcenásek M, et al. TVT® and TVT®-O for surgical treatment of primary stress urinary incontinence: prospective randomized trial. Int Urogynecol J Pelvic Floor Dysfunct 2010; 21(2):141–148
21. Meschia M, Bertozzi R, Pifarotti P et al. Peri-operative morbidity and early results of a randomised trial comparing TVT® and TVT®-O. Int Urogynecol J Pelvic Floor Dysfunct 2007; 18(11):1257–1261
22. Ross S, Robert M, Swaby C et al. Tension-Free vaginal tape for stress. Obstet Gynecol 2009; 114(6):1287–1294
23. Schraffordt Koops SE, Bisseling TM, Heintz AP, et al. Quality of life before and after TVT®, a prospective multicentre cohort study, results from the Netherlands TVT® database. BJOG 2006; An Int J Obstet Gynaecol 113(1):26–29
24. Valpas A, Kivelä A, Penttinen J, et al. Tension-free vaginal tape and laparoscopic mesh colposuspension for stress urinary incontinence. Obstet Gynecol 2004; 104(1):42–49
25. Wang F, Song Y, Huang H Prospective randomized trial of TVT® and TOT as primary treatment for

female stress urinary incontinence with or without pelvic organ prolapse in Southeast China. Arch Gynecol Obstet 2009; 281(2):279–286

26. Ward K, Hilton P Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. BMJ (Clin Res edition) 2002; 325(7355):67
27. Tomoe H, Kondo A, Takei M, et al. Quality of life assessments in women operated on by tension-free vaginal tape (TVT®). Int Urogynecol J Pelvic Floor Dysfunct 2005; 16(2):114–118, 27.
28. Bø K, Talseth T, Vinsnes A Randomized controlled trial on the effect of pelvic floor muscle training on quality of life and sexual problems in genuine stress incontinent women. Acta Obstet Gynecol Scand 2000; 79(7):598–603
29. Gilling PJ, Wilson LC, Westenberg AM et al. A doubleblind randomized controlled trial of electromagnetic stimulation of the pelvic floor vs sham therapy in the treatment of women with stress urinary incontinence. BJU Int 2009; 103(10):1386–1390
30. Neumann PB, Grimmer KA, Grant RE, et al. Physiotherapy for female stress urinary incontinence: a multicentre observational study. Aust N Z J Obstet Gynaecol 2005; 45(3):226–232
31. Hinoul P, Roovers JPWR, Ombelet W, et al. Surgical management of urinary stress incontinence in women: a historical and clinical overview. Eur J Obstet Gynecol Reprod Biol 2009; 145(2):219–225
32. Latthe PM, Foon R, Toozs-Hobson P Transobturator and retropubic tape procedures in stress urinary incontinence: a systematic review and meta-analysis of effectiveness and complications. BJOG 2007; An Int J Obstet Gynaecol 114(5):522–531
33. Guyatt GH, Feeny DH, Patrick DL Measuring healthrelated quality of life. Ann Intern Med 1993; 118(8):622–629
34. Barnett AG, van der Pols JC, Dobson AJ Regression to the mean: what it is and how to deal with it. Int J Epidemiol 2005; 34 (1):215–220
35. Novara G, Ficarra V, Boscolo-Berto R, et al. Tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials of effectiveness. Eur Urol 2007; 52(3):663–678
36. Dumoulin C, Hay-Smith J Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane database of systematic reviews 2010; (1):CD005654
37. Ogah J, Cody J, Rogerson L Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane database of systematic reviews 2010; (1):CD006375
38. Labrie J, van der Graaf Y, Buskens E, et al. Protocol for Physiotherapy or TVT® Randomised Efficacy Trial (PORTRET): a multicentre randomised controlled trial to assess the cost-effectiveness of the tension free vaginal tape versus pelvic floor muscle training in women with symptomatic moderate to severe stress urinary incontinence. BMC Women's Health 2009; 9(2)


3

PROTOCOL FOR PHYSIOTHERAPY OR TVT RANDOMISED EFFICACY TRIAL (PORTRET): A MULTICENTRE RANDOMISED CONTROLLED TRIAL TO ASSESS THE COST-EFFECTIVENESS OF THE TENSION FREE VAGINAL TAPE VERSUS PELVIC FLOOR MUSCLE TRAINING IN WOMEN WITH SYMPTOMATIC MODERATE TO SEVERE STRESS URINARY INCONTINENCE

J. Labrie, Y. van der Graaf, E. Buskens, E.S.M. Tiersma and C.H. van der Vaart

BMC Women's Health. 2009 Sep 1;9:24

ABSTRACT

Background

Stress urinary incontinence is a common condition affecting approximately 20% of adult women causing substantial individual (quality of life) and economic (119 million Euro/year spent on incontinence pads in the Netherlands) burden. Pelvic floor muscle training (physiotherapy) is regarded as first line treatment, but only 15-25% of women will be completely cured. Approximately 65% will report that their condition Improved, but long-term adherence to treatment is problematic. In addition, at longer term (2-15 years) follow-up 30-50% of patients will end up having slingsurgery. From 1996 a minimal invasive surgical procedure, the Tension-free Vaginal Tape (TVT®) has rapidly become the gold standard in surgical treatment of stress urinary incontinence. With TVT 65-95% of women are cured. However, approximately 3-6% of women will develop symptoms of an overactive bladder, resulting in reduced quality of life. Because of its efficacy the TVT appears to be preferable over physiotherapy but both treatments and their costs have not been compared head-to-head in a randomised clinical trial.

Methods

A multi-centre randomised controlled trial will be performed for women between 35 - 80 years old with moderate to severe, predominantly stress, urinary incontinence, who have not received specialised physiotherapy or previous anti incontinence surgery. Women will be assigned to either physiotherapy by a specialised physiotherapist for a standard of 9-18 session in a period of 6 months, or TVT(O)® surgery. The main endpoint of the study is the subjective improvement of urinary incontinence. As secondary outcome the objective cure will be assessed from history and clinical parameters. Subjective improvement in quality of life will be measured by generic (EQ-5D) and disease-specific (Urinary Distress Inventory and Incontinence Impact Questionnaire) quality of life instruments. The economical endpoint is short-term (1-year) incremental cost-effectiveness in terms of costs per additional year free of urinary incontinence and costs per Quality Adjusted Life Years (QALY) gained. Finally, treatment strategy and patient characteristics will be combined in a prediction model, to allow for individual treatment decisions in future patients. Four hundred female patients will be recruited from over 30 hospitals in the Netherlands

BACKGROUND

Urinary incontinence is a common problem among adult women, with an estimated overall prevalence of 40% and between 6-10% of women with severe incontinence.[1] Stress urinary incontinence is the predominant type of incontinence affecting approximately 50% of incontinent women. Thus, 20% of adult women will experience stress urinary incontinence. The severity of urinary incontinence is often expressed in the number of incontinence episodes/week, where 7-14 episodes/week is considered as moderate and more than 14 episodes/week as severe incontinence.[1]

In addition, urinary incontinence is known to have a negative impact on quality of life and the economical costs related to it are substantial. These patient-centred and economical outcomes are important. For the treatment of stress urinary incontinence there are two options: pelvic floor muscle training (physiotherapy) and slingsurgery. physiotherapy is currently advised as primary treatment, because it is statistically significant more likely to improve incontinence symptoms as compared to no or sham physiotherapy (OR 1.42, 95%CI 1.28-1.58).[2] Approximately 65% of women treated with physiotherapy experience improvement of their incontinence. However, a 100% cure rate (no incontinence episodes) is recorded in only 15 to 28% of women.[3,4] In addition to the low percentage of objective cure, the long-term efficacy of physiotherapy is under debate. After a 3-15 year follow-up, 25-50% of women primarily treated with physiotherapy have undergone slingsurgery.[5-7] This can be due to lack of persistent efficacy, but may also be related to lack of compliance with the physiotherapy program.

In the past decade, surgery for stress incontinence has made a huge progression with the introduction of minimally invasive surgical techniques. The Tension-free Vaginal Tape (TVT®) and Tension-free Vaginal Tape Obturator (TVT-O®) are the most frequently performed procedures. In both cases, a small incision is made under the mid urethra through which a polypropylene mesh is placed without tension under the urethra. If abdominal pressure increases, the urethra is compressed to the tape and continence is restored. An advantage of these procedures is that they can be performed in day-care.[8] After a TVT® procedure approximately 66% of women are completely cured (100% dry) and 80-95% of women show an improvement.[9] Furthermore, this effect seems to be longstanding. However, although minimal invasive, stress incontinence surgery carries a risk of complications. Major complications are extremely rare with an incidence of 0.007% for bowel perforation and 0.012% for vascular injury.[8] The most common complication of bladder perforation during the procedure (approximately 3-6% for TVT and below 1% for TVT-O is easily recognised during the procedure itself and carries no long-term morbidity. Adverse outcome of slingsurgery in terms of the development of new symptoms may be a bigger concern. Voiding difficulties and symptoms of an overactive bladder are reported in 6% of cases.[9]

In the Netherlands women are usually seen by the general practitioner (GP) first. The GP Dutch guidelines (revised version 2006) on stress incontinence advocate to either start treatment with physiotherapy with instructions of the GP, or to refer to a specialised physiotherapist. In 2001 the Health Counsel reported that only 1.6% of women were referred to a physiotherapist.[10] Thus, the majority of incontinent women were not referred to specialised therapy. Treatment by the GP consists of giving verbal and written instructions (as is described

in their guideline) how to contract and train the pelvic floor, with first revision after 3 months. This is clearly different from the weekly, individual sessions given by a specialised (biofeedback) physiotherapist. If treatment by the GP fails, it is advocated to refer the woman for specialised physiotherapy physiotherapy. This is the group of women where our study aims at.

The main objective of our study is to answer the question whether it is more (cost) effective to refer for specialised physiotherapy or for TVT-O surgery after the standard initial instruction and training given by the GP has failed.

Primary slingsurgery in this group of patients may be cost effective when compared to physiotherapy as its cure rate is higher. A comparison of both strategies has been performed in a small sample of patients comparing abdominal Burch surgical procedure versus physiotherapy.[11] Although this single study concluded that primary slingsurgery was preferable, the design and power did not meet the standards to provide sufficient scientific evidence. Finally, it is unclear which factors are associated with success or failure of physiotherapy and TVT. After identification of these factors a prediction model can be built that can further individualise treatment. In addition to our cost-effectiveness analyses we aim to develop such a prediction model.

METHODS

Study Aims

The primary aim of the PORTRET study is to compare the clinical and cost-effectiveness of physiotherapy versus the TVT/ TVT-O procedure as treatment for moderate to severe stress urinary incontinence.

Study design and setting

The PORTRET study is a multidisciplinary, multicentre non-blinded therapeutic randomised controlled trial. Randomisation will be performed centrally with computerised randomisation tables. The two trial arms are physiotherapy by a specialised physiotherapist and a surgical intervention with the TVT or TVT-O. Recent data show that both the TVT and TVT-O are equally effective.[12,13] For obvious reasons blinding of treatment between physiotherapy and slingsurgery will not be possible. To reflect daily practice as close as possible the assessment of costs will start directly after randomisation. We expect that the maximum effect of physiotherapy will be reached within 3-6 months. To account for possible changes in symptoms and changes in costs during this period, cost and symptom assessments are made every two months by means of a telephone-administered questionnaire during the first 4 months. After that an assessment at 6, 12 and 18 months is performed. From literature, one of the predictive factors for the efficacy of treatment is the severity of incontinence at baseline. Therefore, we will introduce stratification by severity into the randomisation. We will stratify according to the severity (moderate or severe) as established by the Sandvik index (**Table 1**).[14] The flowchart and study design are presented in **Figure 1** and **Table 2**

Table 1. Sandvik Index

SANDVIK INDEX	Quantity of urine loss	
	1 = drops	2 = more than drops
Episodes		
1 = < 1 time a month	1	2
2 = 1 to more times a month	2	4
3 = 1 to more times a week	3	6
4 = daily	4	8

1-2 points; mild incontinence, 3-4 points; moderate incontinence 6-8 points; severe incontinence

Ethical consideration

The study was approved by the medical ethical review board of the Universitary Medical Centre Utrecht (METC UMCU 07/278). Full medical ethical approval has been obtained on 05-02-2008.

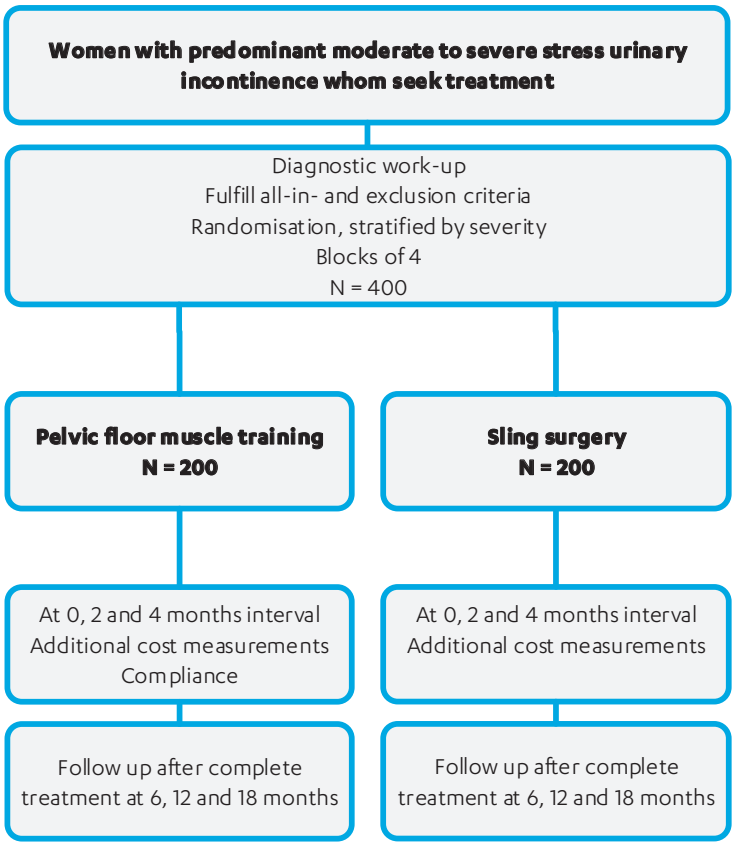


Figure 1. Flowchart

Identification and determination of eligible patients

All women aged 35-80 years whom present with symptomatic moderate to severe, according to the Sandvik severity index (**Table 1**), predominant stress urinary incontinence, will be considered for inclusion.[14] They should present themselves with the problem of incontinence to their general practitioner, gynaecologist or urologist. They should not have already been referred for specialised pelvic floor muscle training.

The predominance of SUI is assessed with the Stress/Urge Incontinence Questionnaire (S/UIQ). Two questions are asked. "How many times in the last seven days have you had an accidental leakage of urine onto your clothing, underwear, or pad?".

- During an activity such as coughing, sneezing, laughing, running, exercising or lifting? Symptom of stress urinary incontinence (SUI).
- With a sudden strong need to pass water that you could not reach the toilet in time? Symptom of urge urinary incontinence (UUI).

For predominant stress urinary incontinence the number of SUI events should outnumber the number of UUI.

Urodynamic testing will not be used in this study, unless the physician decides this is necessary. Its sensitivity, specificity and predictive value for diagnosing and predicting outcome in female urinary incontinence has not been proved.[15] So no exclusion criteria will be based on urodynamic assessments (if performed).

SUI must have been demonstrated on physical examination or on urodynamic assessment if performed. Patients will be excluded in case of previous incontinence surgery, pelvic organ prolapse stadium 2 or higher according to POP-Q classification or in case of residual post voiding bladder volume of more than 100 ml on catheterisation or ultrasound (Bladderscan®)

Study Interventions

After obtaining informed consent, eligible women will be assigned to either physiotherapy by a specialised physiotherapist for a standard of 9-18 sessions in a period of 6 months, or TVT(O)® surgery.

Randomisation

After checking the inclusion criteria an eligible patient is asked if she might be willing to participate and will receive written and verbal information about the study. A new appointment with the research nurse will be made. After an interval of one week the research nurse will ask if the patients wants to participate in the study and the exclusion criteria are checked. This will be undertaken by the research nurse, not by the medical specialist him/herself. If an eligible patient wants to cooperate she is asked to sign the informed consent. When in- and exclusion criteria are met, randomisation will take place. Study inclusion and exclusion criteria are presented in **Figure 2**.

Randomisation will be performed with the use of computerised randomisation tables. The randomisation will be stratified according to the severity of incontinence (moderate or severe as established by the Sandvik index. For obvious reasons (slingsurgery versus conservative

treatment) both the randomisation outcome and the personal involved in outcome assessment cannot be blinded.

Patient follow-up procedures

Patients will be followed from the start of primary therapy until 18 months later. Follow-up will consist of various elements For all patients the next items will be recorded at inclusion:

1. Baseline characteristics
2. History and clinical examination
3. 48 h-bladder (voiding and incontinence) diary
4. 24 h-padtest
5. Validated Quality of Life questionnaires (Urinary Distress Inventory, Incontinence Impact Questionnaire, Euroqol 5D, patient global impression of severity/ improvement)
6. Uroflow measurement including post void residual volume
7. Cost-analysis questionnaire

The onset of primary therapy, either TVT(O)® in the slingsurgery arm of the study or physiotherapy in the physiotherapy arm of the study will be T = 0

Table 2. Study Design Schedule

	Baseline visit	Rando-misation	Study entry	2, 4 months*	6 months	12 months	18 months
Patient characteristics	X						
Gynaecologic examination	X					X	
Assessment of pelvic floor functioning	X				X	X	
48 hour bladder diary	X	**Checking**			X	X	
Flow	X				X	X	
Residual volume	X	**Inclusion**			X	X	
Stress test	X				X	X	
Sandvik index	X	**&**			X	X	
24 hour pad test	X					X	
Global Impression of severity	X	**Exclusion**		X	X	X	X
Global Impression of improvement				X	X	X	X
EuroQol 5D		**Criteria**	X		X	X	X
UDI	X				X	X	X
IIQ	X				X	X	X
Costs assessment			X	X	X	X	X
Compliance with treatment[1]				X		X	
Complications of slingsurgery[1]				X			

[1] Compliance is measured for the physiotherapy group only
[2] Complications are only measured in women undergoing slingsurgery.
UDI: Urogenital Distress Inventory; IIQ: Incontinence Impact Questionnaire

In case of slingsurgery, the patient will receive the standard care associated with the pre-, per- and postoperative standards of the participating hospital. She will visit the hospital after surgery at 6 weeks, 6, 12 and 18 months. Questionnaires will be handed out at these visits containing the items mentioned above. Furthermore, special attention will be given with respect to extra visits to the general practioner; physiotherapist or specialist visits in relation to the surgical procedure that might have taken place and physical examination will be performed. Costs associated with incontinence and therapy will also be assessed with telephone-administered questionnaires at 2 and 4 months follow-up. Women who are enrolled for physiotherapy will be followed-up according to the same schedule besides the 6 weeks postoperative check-up.

Patient outcome measures

This study will compare the clinical and cost-effectiveness of physiotherapy versus the TVT/ TVT-O procedure as treatment for moderate to severe stress urinary incontinence.

Primary outcome: Subjective improvement of urinary incontinence

Secondary outcome(s):

1. Complete cure on objective and subjective parameters.
2. Subjective improvement in generic and disease-specific quality of life.
3. Complications and de novo urogenital symptoms.
4. The incremental cost-effectiveness of TVT® as compared to physiotherapy, accounting for direct and indirect costs parameters.
5. Development of a prediction model for successful treatment, with the therapy given (physiotherapy or TVT®) as independent variable in the model.

Study inclusion and exclusion criteria

Inclusion criteria

- Women aged 35-80 years
- Symptoms of moderate to severe, predominant stress urinary incontinence.
- Confirmation of stress urinary incontinence during gynaecological examination and /or urodynamics
- Sandvik index ≥ 3

Exclusion criteria

- Post voiding bladder volume > 100 ml, on bladder catheterisation or ultrasound (Bladderscan®)
- History of anti-incontinence surgery
- Pelvic Floor Muscle Training (physiotherapy) in the previous 6 months
- Genital prolapse Stage 2 or more (POP-Q classification)
- Patients desire for future pregnancy and childbirth
- Co-morbidity which is associated with increased surgical risks
- History of recurrent lower urinary tract infection (> 3 times/year)
- Insufficient knowledge or understanding of the Dutch language
- The use of medication that may affect bladder function.
- History of or current major psychiatric illness.
- History of chronic neurological disease.

Figure 2. Study inclusion and exclusion criteria

Sample size considerations

Literature shows a subjective improvement of incontinence after physiotherapy up to 65%, and a subjective improvement after TVT(O)® of at least 80%. In order to detect this difference with a power of 0.9 and an alpha of 0.05, we need 200 women in each trial arm. For our primary outcome parameter, total cure of incontinence, the expected difference between both arms is much larger: 28% cure after physiotherapy, and 65% cure after TVT. The 200 women in each treatment arm will be largely sufficient to assess a statistically significant difference in this secondary outcome.

Sample size calculation for the prediction models is based on the number of successes (or failures). For each predictor in the model we need 10-15 successes. Our predefined prediction model consists of 5 predictors and the interaction terms with treatment. Our total sample size will exist of 400 women. The expected number of successes (cure) of the physiotherapy group is 30 (15% of 200) women, the number of women cured after TVT® is an estimated 130 (65% of 200 women). So the total number of complete cure is an estimated 160 women, with 240 women being not completely cured. These figures are sufficient for modelling up to 10-12 predefined possible predictors of cure. With respect to subjective improvement an estimated total of 290 women will show subjective improvement as measured with the Patient Global Impression of Improvement (PGI-I) questionnaire (65% of 200 women with physiotherapy plus 80% of 200 women in TVT® group). Thus, 110 women can be considered failures. Again, this also allows us to make a prediction model for improvement with the predefined predictors. Therefore the study sample will also be amply sufficient for prediction purposes.

Economic evaluation

In accordance with the primary aim of the clinical trial, the primary outcome for the economic evaluation will be the number of women with satisfactory results, i.e., subjectively improved, at 6, 12 and 18 months. During the period that women allocated to physiotherapy follow their training program, women whom underwent TVT(O)® may already experience a period with satisfactory outcome. This time aspect will be accounted for by estimating and comparing person time with satisfactory results.

Health related quality of life (HRQoL) is considered an important outcome. In addition to the disease specific questionnaires (UDI and IIQ), two global questions, Patient Global Impression of Severity and Patient Global Impression of Improvement, (PGI-S and PGI-I), and a generic questionnaire, Euroqol 5D (EQ-5D) will be filled out at baseline and at regular intervals up to twelve months after completion of treatment. Using the EQ5D the outcome in terms of quality adjusted life years (QALYs) can be estimated. The effects observed by means of the disease specific questionnaire will be reported separately.[16-18]

Costs of the strategies directly TVT(O)® as well as physiotherapy will be estimated using a societal perspective. Accordingly, direct medical costs will be based on the actual costs of the personnel and other resources used such as incontinence pads. Unit costs will be based on a specific costing study conducted in the hospital setting and the primary care setting. Where available unit costs will be based on the standard prices published in the current guidelines.

Also, as physiotherapy is much more time consuming for the patients the costs associated to sick leave at work will be estimated using the friction cost method. The hours women spend on travel and training etc. will be assessed by questionnaires and subsequently valued.

Cost-effectiveness

The incremental costs per QALY gained will be estimated at one year. Uncertainty will be evaluated using standard bootstrap techniques (1,000 replicates). The incremental costs and effects will be depicted in a cost-effectiveness analysis plane. The resulting scatter plot provides information directly interpretable as the probability of one intervention being cost-effective compared to the alternative.

Statistical analysis

Data will be presented as numbers (percentage) for nominal variables or means (standard deviation) for interval variables. Differences between the two interventions will be analysed based on intention-to-treat analysis. For interval variables, differences between the two groups will be analysed with a Students t-test, proportions will be compared using the Chi-square test.

Multivariate logistic regression analysis will be used for the development of the prediction of successful treatment only. In literature, a wide range of patient characteristics were considered to be associated with the outcome of physiotherapy. In the Consultation on Incontinence (ICI) proceedings it was concluded that there are no reliable factors identified yet, because the number of observations and studies is too low.[2] However, several factors have been identified as possible predictors of a successful outcome after physiotherapy. To provide information on treatment effectiveness in different subgroups of patients participating in this trial, we will derive a prediction model and estimate interaction of treatment effect with baseline incontinence severity (number of leaks/week), duration of symptoms, increasing parity, Body Mass Index, baseline pelvic floor contraction ability, and treatment modality as factors.[2] The defined prediction model will therefore be pre-specified resulting in less over-optimism than models in which the choice of predictors is strongly driven by the data-set and the need for external validation.[19] From the multivariate logistic model, in which success will be defined as cure (no objective or subjective incontinence) at 12 and 18 months follow-up, we will estimate the weight of the different coefficients. The modelling process will be internally validated by bootstrap resampling. This technique gives an impression of how "over-optimistic" the model is i.e., how much the performance of the model may deteriorate when applied to a new group of similar patients.[20]

Time plan

Patient recruitment started in March 2008 and is planned to continue until December 2009. The follow-up period is 18 months, and therefore will continue until June 2011. The study is conducted in cooperation with the urogynaecology consortium of the Netherlands. Most participating clinics have disposition over a research nurse for follow-up and data collection in order to fill out the web-based case record forms.

Knowledge transfer

Outcomes of the PORTRET trial will be important for reconsidering the added value of prescribing physiotherapy to every patient with stress-incontinence as primary treatment, as well as comparing objective and subjective treatment success or failure between TVT® and physiotherapy. The results of this study will be submitted to different international and national scientific associations such as the International Continence Society (ICS).

REFERENCES

1. Hunskaar S, Burgio K, Diokno A, et al. Epidemiology of urinary and faecal incontinence and pelvic organ prolapse. In Incontinence Volume 1, basic evaluation 3rd International Consultation on Incontinence edition. Paris: Health publication Ltd;2005.
2. Wilson PD, Hay-Smith J, et al. Adult Conservative management. In Incontinence Volume 2, management 3rd International Consultation on Incontinence edition. Paris: Health publication Ltd; 2005.
3. Alewijnse D, Metsemakers JF, Mesters IE, et al. Effectiveness of pelvic floor muscle exercise therapy supplemented with a health education program to promote longterm adherence among women with urinary incontinence. Neurourol Urodyn 2003; 22(4):284-295.
4. Goode PS, Burgio KL, Locher JL, et al. Effect of behavioral training with or without pelvic floor electrical stimulation on stress incontinence in women: a randomized controlled trial. JAMA 2003; 290(3):345-352.
5. Cammu H, Van Nylen M, Blockeel C, et al. Who will benefit from pelvic floor muscle training for stress urinary incontinence? Am J Obstet Gynecol 2004; 191(4):1152-1157.
6. Bo K, Kvarstein B, Nygaard I. Lower urinary tract symptoms and pelvic floor muscle exercise adherence after 15 years. Obstet Gynecol 2005; 105(5 Pt 1):999-1005.
7. Lamers BH, Vaart CH van der. Medium-term efficacy of pelvic floor muscle training for female urinary incontinence in daily practice. Int Urogynecol J Pelvic Floor Dysfunct 2007; 18(3):301-307.
8. Atherton MJ, Stanton SL. The tension-free vaginal tape reviewed: an evidence-based review from inception to current status. BJOG 2005; 112(5):534-546.
9. Ward K, Hilton P. United Kingdom and Ireland Tension-free Vaginal Tape Trial Group: Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. BMJ 2002; 325(7355):67.
10. Gezondheidsraad Den Haag: Urine Incontinentie. 2001; 2001/12: [http://www.gezondheidsraad.nl/nl/adviezen/urine-incontinentie].
11. Klarskov P, Belving D, Bischoff N, et al. Pelvic floor exercise versus surgery for female urinary stress incontinence. Urol Int 1986; 41(2):129-132.
12. Laurikainen E, Valpas A, Kivela A, et al. Nilsson CG: Retropubic compared with transobturator tape placement in treatment of urinary incontinence: a randomized controlled trial. Obstet Gynecol 2007; 109(1):4-11.
13. Liapis A, Bakas P, Giner M, et al. Tension-free vaginal tape versus tension-free vaginal tape obturator in women with stress urinary incontinence. Gynecol Obstet Invest 2006; 62(3):160-164.
14. Sandvik H, Seim A, Vanvik A, et al. A severity index for epidemiological surveys of female urinary incontinence: comparison with 48-hour pad-weighing tests. Neurourol Urodyn 2000; 19(2):137-145.
15. Payne C, Blaivas J, et al. Research methodology. In Incontinence Volume 1, basic evaluation 3rd International Consultation on Incontinence edition. Paris: Health publication Ltd; 2005.
16. Yalcin I, Bump RC: Validation of two global impression questionnaires for incontinence. Am J Obstet Gynecol 2003; 189(1):98-101.
17. Vaart CH van der, de Leeuw JR, Roovers JPWR, et al. Measuring health-related quality of life in women with urogenital dysfunction: the urogenital distress inventory and incontinence impact questionnaire revisited. Neurourol Urodyn 2003; 22(2):97-104.
18. Brooks R: EuroQol: the current state of play. Health Policy Glasgow, Scotland, UK 1996; 37(1):53-72.
19. Harrell FE: Regression model strategies New York: Springer-Verlag; 2001.
20. Harrell FE Jr, Lee KL, Matchar DB, et al. Regression models for prognostic prediction: advantages, problems, and suggested solutions. Cancer Treat Rep 1985; 69(10):1071-1077.


4

SURGERY VERSUS PHYSIOTHERAPY FOR STRESS URINARY INCONTINENCE

J. Labrie, L.C.M. Berghmans, K Fischer, A.L. Milani, I. van der Wijk, D.J.C. Smalbraak, A. Vollebregt, R.P. Schellart, G.C.M. Graziosi, J.M. van der Ploeg, J.F.G.M. Brouns, E.S.M. Tiersma, A.G. Groenendijk, P.C. Scholten, B.W.J. Mol, E.E. Blokhuis, A.H. Adriaanse, A. Schram, J.P.W.R. Roovers, A.L.M. Lagro-Janssen and C.H. van der Vaart

N Engl J Med 2013;369;12:1124-33

ABSTRACT

Background

Physiotherapy involving pelvic-floor muscle training is advocated as first-line treatment for stress urinary incontinence; midurethral-sling surgery is generally recommended when physiotherapy is unsuccessful. Data are lacking from randomised trials comparing these two options as initial therapy.

Methods

We performed a multicentre, randomised trial to compare physiotherapy and midurethral-sling surgery in women with stress urinary incontinence. Crossover between groups was allowed. The primary outcome was subjective improvement, measured by means of the Patient Global Impression of Improvement at 12 months.

Results

We randomly assigned 230 women to the surgery group and 230 women to the physiotherapy group. A total of 49.0% of women in the physiotherapy group and 11.2% of women in the surgery group crossed over to the alternative treatment. In an intention-to-treat analysis, subjective improvement was reported by 90.8% of women in the surgery group and 64.4% of women in the physiotherapy group (absolute difference, 26.4 percentage points; 95% confidence interval [CI], 18.1 to 34.5). The rates of subjective cure were 85.2% in the surgery group and 53.4% in the physiotherapy group (absolute difference, 31.8 percentage points; 95% CI, 22.6 to 40.3); rates of objective cure were 76.5% and 58.8%, respectively (absolute difference, 17.8 percentage points; 95% CI, 7.9 to 27.3). A post hoc per-protocol analysis showed that women who crossed over to the surgery group had outcomes similar to those of women initially assigned to surgery and that both these groups had outcomes superior to those of women who did not cross over to surgery.

Conclusion

For women with stress urinary incontinence, initial midurethral-sling surgery, as compared with initial physiotherapy, results in higher rates of subjective improvement and subjective and objective cure at 1 year. (Funded by ZonMw, the Netherlands Organisation for Health Research and Development; Dutch Trial Register number, NTR1248.)

INTRODUCTION

Stress urinary incontinence is a common health problem among women that negatively affects quality of life.[1-3] The International Consultation on Incontinence defines stress urinary incontinence as an involuntary loss of urine on physical exertion, sneezing, or coughing.[4] Pelvic-floor muscle training (physiotherapy) is generally regarded as first-line management for the condition.[5] However, physiotherapy is associated with broad variation in the rates of subjective success (53 to 97%) and objective success (5 to 49%), and more severe symptoms are associated with worse outcomes.[6,7] After 3 to 15 years, 25 to 50% of women initially treated with physiotherapy have proceeded to surgery.[7-9] Midurethral-sling surgery is a minimally invasive surgical technique for the treatment of stress urinary incontinence,[10] with subjective cure rates between 75% and 94% and objective cure rates between 57% and 92%.[1,11,12] The procedure is regarded as effective, with minimal complications.[11]

The difference in the reported frequencies of a successful outcome between surgery and physiotherapy raises the question of whether all women with moderate-to-severe stress-predominant urinary incontinence should initially be treated with physiotherapy or should immediately undergo surgery as initial treatment. Midurethral-sling surgery and physiotherapy have not been directly compared. We therefore conducted a multicentre, pragmatic, randomised trial to compare initial midurethral-sling surgery with initial physiotherapy in women with moderate-to severe stress urinary incontinence, using standardised outcome measures at 12 months.

METHODS

Study Design

We performed our randomised trial at 4 university medical centers and 19 general hospitals (24% of Dutch hospitals). The study protocol and inclusion and exclusion criteria have been published previously.[13] In brief, eligible women were 35 to 80 years of age and had been referred to an outpatient gynecology or urology clinic after presenting with stress urinary incontinence classified as moderate or severe according to the severity index developed by Sandvik et al.[14] (**Supplementary Table 1**) In women presenting with mixed incontinence (involuntary loss of urine associated with urgency [urge incontinence] and also on physical exertion, sneezing, or coughing), stress incontinence was classified as predominant if there were more episodes of stress than urge incontinence, as reported on the validated Dutch version of the Urogenital Distress Inventory.[13] Women included in the study either had not received treatment or had undergone physiotherapy more than 6 months before randomisation. The diagnosis of stress urinary incontinence was based on a demonstration of leakage of urine on straining or coughing at a bladder volume of at least 300 ml. Urodynamic testing to confirm the diagnosis was not mandatory for eligibility.[15] Women who had undergone previous incontinence surgery or who had concomitant pelvic organ prolapse of stage 2 or higher (according to the Pelvic Organ Prolapse Quantification system) were excluded.[4]

The ethics committee of the Utrecht Medical Centre and the institutional review boards at the individual sites approved the study protocol. The last author assumes responsibility for

the completeness and accuracy of the data and analyses and for the fidelity of the study to the protocol. The trial was initiated and performed without the support or involvement of manufacturers of midurethral slings.

After written informed consent was obtained, research nurses on site performed computerised randomisation on a central server. An independent data manager designed the randomisation table. Women were assigned in a 1:1 ratio to the surgery group or the physiotherapy group, with blocks of four per centre, stratified according to the severity of incontinence (moderate or severe). The treatment assignments were not concealed.

Surgical procedures were performed by 49 gynecologists and urologists. Before participating in this trial, each surgeon had performed a minimum of 20 procedures. Both retropubic and transobturator midurethral-sling surgical techniques were allowed.[10,16]

Physiotherapy was performed by 83 (17%) of the 478 certified pelvic physiotherapists in the Netherlands. Pelvic-floor muscle training for stress urinary incontinence was performed according to the Dutch guidelines.[17] Women were educated about the function of the pelvic-floor muscles, bladder function, and how to perform a correct pelvic-floor muscle contraction. They were also taught to perform a short muscle contraction before an increase in intra abdominal pressure, such as that associated with sneezing.[18]

A supervised program to help women build up to 8 to 12 maximal contractions three times per day was provided. Treatment was given at 1-week or 2-week intervals, depending on the severity of symptoms, treatment goals, adherence, and the ability of the women to learn to perform the muscle contractions. The physiotherapist determined the number of sessions, with an intended number of nine sessions in 9 to 18 weeks (the standard number at the time). If a woman was unable to contract her pelvic-floor muscles, touch, tapping, and massage were applied to increase awareness of these muscles. Biofeedback-assisted or functional electrostimulation therapy could be used. If a woman was dissatisfied with the result of the assigned treatment, she was allowed to cross over to the alternative treatment, which is consistent with usual clinical practice, but data were analysed according to the intention-to-treat principle.

Outcomes

The primary outcome was subjective improvement in symptoms of stress urinary incontinence at 12 months, measured with the use of the Patient Global Impression of Improvement (PGI-I) instrument, a 7-point Likert scale that ranks the response to a single question from "very much worse" to "very much better." The PGI-I response has been shown to correlate significantly with the frequency of incontinence episodes, cough-test results, pad-test results, and scores on several Incontinence Quality of Life questionnaires.[19,20] In concordance with other studies, improvement was considered to be clinically significant if the patient's response was "much better" or "very much better."[21-23] The PGI-I response was also assessed at 2, 4, 6, and 18 months to monitor changes.

The secondary outcomes included urogenital symptom improvement; disease-specific quality of life; objective and subjective cure of stress urinary incontinence; and adverse events, including new urinary symptoms. Urogenital symptoms and disease-specific quality of life were measured with the validated Dutch versions of the urogenital Distress Inventory (UDI) and the

Incontinence Impact Questionnaire (IIQ), respectively. [24,25] The domain scores range from 0 to 100, with lower scores indicating less distress caused by urogenital symptoms (UDI) and better quality of life (IIQ). The Patient Global Impression of Severity (PGI-S) index was used to assess changes in the perceived severity of incontinence on a 4-point Likert scale. Responses were dichotomised into no symptoms and symptoms (mild, moderate, or severe).[19] Subjective cure of stress urinary incontinence was defined as a negative response to the question, "Do you experience urine leakage related to physical activity, coughing, or sneezing?" Objective cure was defined as no incontinence observed during a cough stress test at a bladder volume of at least 300 ml.

A standardised case-report form was used to record adverse events peri-operatively for women undergoing surgery and at each follow-up visit for all women. Data were collected at baseline (either the day of surgery or the first physiotherapy session) and at 2, 4, 6, 12, and 18 months by 13 research nurses covering all clinical sites. Data collection was performed on a standardised, computerised, secured case-record form accessible online and was controlled by an independent data-management centre. The cough test was performed at the clinical evaluation at 12 months.

Statistical Analysis

On the basis of the assumption that 80% of women in the surgery group and 65% of women in the physiotherapy group would report subjective improvement,[13] we calculated that 197 women were needed in each group to achieve a power of 90% (at a two-sided significance level of 5%). Anticipating a 15% loss to follow-up, we planned to include 460 women.

We performed a modified intention-to-treat analysis, which included all women who underwent initial surgery as the assigned treatment or who started initial physiotherapy as the assigned treatment. In cases of crossover between treatment groups, the data were analysed according to the assigned treatment. The main analysis was performed with the original data and was repeated after imputation of missing data (sensitivity analysis). To impute missing data, a multiple imputation model with 10 iterations using predictive mean matching was applied.[26]

Descriptive statistics were used to analyse baseline characteristics. Treatment effects on binary variables (PGI-I [improvement], PGI-S [no symptoms], subjective cure, and objective cure) are presented as the absolute change in percentage points between groups. The 95% confidence intervals were calculated with the use of the Newcombe–Wilson method for interval estimation, and Fisher's exact test was used for calculating the significance level.[27] Student's t-test was used to compare continuous data between groups. Changes in UDI and IIQ domain scores over time were analysed with the use of a paired-samples Student's t-test. To facilitate interpretation of changes in UDI and IIQ scores, effect sizes were calculated with the use of Cohen's D test. An effect size of 0.3 or less was considered small, more than 0.3 to 0.8 moderate, and more than 0.8 large.[28]

A post hoc per-protocol analysis of outcomes among women who underwent physiotherapy only, women who underwent surgery after physiotherapy, and women who underwent initial surgery was performed with the use of one-way analysis of variance and paired t-tests with Holm's Bonferroni correction for multiple comparisons. All statistical analyses were performed with the use of SPSS Statistics for Windows, version 17.0 (SPSS).

RESULTS

Study Population

During the period from March 2008 through May 2010, a total of 656 women with stress urinary incontinence or mixed urinary incontinence in which stress incontinence was predominant were asked to participate in the study, of whom 460 gave written informed consent. These women were randomly assigned to the surgery group (230) or the physiotherapy group (230) (**Figure 1**).

Figure 1. Randomisation and Follow-up.

Analyses were performed for 215 women assigned to the surgery group and 202 women assigned to the physiotherapy group; at 12 months, outcome data were available for 196 (91.2%) and 174 (86.1%) of these women, respectively (P = 0.11). In the physiotherapy group, 99 women (49.0%) crossed over to the surgery group, after a mean (±SD) time of 31.7±12.7 weeks.

The frequency of crossover to the surgery group was similar among women who had undergone specialised physiotherapy before enrollment and women who had not received previous treatment (47.4% [18 of 38] vs. 49.4% [81 of 164], P = 0.86). Twenty-two women (11.2%) received additional physiotherapy after surgery; these women had symptoms related to pelvic-floor muscle hyperactivity, such as obstructive micturition, and underwent training to relax the pelvic floor muscles.

Intention-to-Treat Analysis

Baseline characteristics and UDI and IIQ domain scores were similar in the two groups (**Table 1**). Primary and secondary outcomes according to the assigned treatment group, for both original and imputed data, are presented in **Table 2**. The PGI-I and PGI-S responses for all follow-up assessments, including the assessment at 18 months, are shown in **Supplementary Table 2**. At 12 months, a significantly higher proportion of women assigned to the surgery group reported improvement, as compared with women assigned to the physiotherapy group; the difference between the groups was 26.4 percentage points (95% confidence interval [CI], 18.1 to 34.5; P<0.001) for the original data and 26.5 percentage points (95% CI, 18.5 to 34.2; P<0.001) when the imputed data were included. Of the 99 women who crossed over from physiotherapy to surgery, 90 (90.9%) reported no improvement on the last PGI-I assessment before surgery was performed. Subjective cure and objective cure of stress urinary incontinence were significantly more frequent in the surgery group than in the physiotherapy group (objective cure, P = 0.001; subjective cure, P<0.001). Treatment effects are shown in **Table 2**.

Both treatment groups had significant improvement in UDI and IIQ domain scores, as compared with baseline values (**Table 2**). Improvements in the UDI scores for incontinence and overactive bladder were significantly greater in the surgery group than in the physiotherapy group (P<0.001 and P = 0.02, respectively, for the original data), but with only moderate effect sizes; the effect sizes were 0.50 (95% CI, −1.6 to 2.6) for incontinence and 0.36 (95% CI, −1.0 to 1.7) for overactive bladder. In the comparison of IIQ domain scores between groups, improvements in mobility and embarrassment scores were significantly greater in the surgery group than in the physiotherapy group (P = 0.001 and P = 0.004, respectively), but again with only moderate effect sizes; effect sizes were 0.34 (95% CI, −1.8 to 2.5) for mobility and 0.31 (95% CI, −2.1 to 2.7) for embarrassment.

Adverse Events

Table 3 summarises adverse events in both groups. A total of 65 adverse events occurred in 41 (9.8%) of 417 women; all adverse events were related to surgery. Intraoperative bladder perforation and vaginal epithelial perforations were successfully treated during surgery without further clinical implications. Three women had a recorded blood loss of 500 ml or more. One woman needed reoperation to loosen the synthetic sling because of persistent voiding problems, and six reoperations were performed for tape exposure.

Table 1. Baseline Characteristics of the Study Population*

Characteristic	Surgery Group (N=215)	Physiotherapy Group (N=202)
Age – yr	50.2±9.8	50.0±8.2
College or university degree – no./total no. (%)	56/211 (26.5)	49/199 (24.6)
Parity		
Median	2	2
Range	0-4	0-7
Current smoker – no./total no. (%)	36/207 (17.4)	37/191 (19.4)
Body-mass Index †	26.4 ±5.0	26.9 ±5.0
Postmenopausal– no./total no. (%)	78/209 (37.3)	67/196 (34.2)
Previous vaginal surgery– no./total no. (%)	41/213 (19.2)	38/202 (18.8)
No. of voidings in 24-hr period‡		
Median	8	8
Range	3-22	3-18
Physiotherapy >6mo before study – no./total no. (%)	34/215 (15.8)	38/202 (18.8)
PGI-S: not severe – no./total no. (%)	9/213 (4.2)	12/196 (6.1)
UDI domain score§		
Urinary Incontinence	42.8 ±19.1	41.1 ±19.2
Overactive Bladder	22.8 ±21.3	18.4 ±20.3
Obstructive Micturition	14.8 ±20.6	11.3 ±18.7
Pain	11.0 ±14.2	9.9 ±14.1
Genital Prolapse	3.9 ±11.6	2.6 ±10.5
IIQ domain scores§		
Physical Functioning	15.3 ±17.5	15.4 ±17.3
Mobility	28.7 ±19.4	27.3 ±20.6
Emotional Health	17.7 ±16.5	18.7 ±18.6
Social Functioning	9.8 ±16.0	11.9 ±20.6
Embarrassment	30.4 ±22.6	±24.1

* Plus-minus values are means ± SD. No significant between-group differences were observed for any characteristic. PGI-S denotes Patient Global Impression of Severity.

† The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were available for 212 women in the surgery group and 193 women in the physiotherapy group.

‡ Data were available for 202 women in the surgery group and 177 women in the physiotherapy group.

§ Domain scores on the Incontinence Impact Questionnaire (IIQ) and the Urogenital Distress Inventory (UDI) range from
0 to 100, with higher scores indicating more distress caused by urogenital symptoms (UDI) or a more negative effect on health-related quality of life (IIQ).[24,25] Data were available for 212 women in the surgery group and 199 women in the physiotherapy group.

Table 2. Primary and Secondary Outcomes in the Surgery and Physiotherapy Groups at 12 Months.*

Outcome	Surgery Group (N = 196)	Physiotherapy Group (N=174)	Original Data	Imputed Data
			Treatment Effect (95% CI)†	
			Percentage points	
PGI-I: improvement – no./total no. (%)	177/195 (90.8)	112/174 (64.4)	26.4 (18.1-34.5)	26.5 (18.5-34.2)
PGI-S: no symptoms – no./total no. (%)	167/195 (85.6)	114/174 (65.5)	20.1 (11.4-28.6)	19.7 (11.4-27.8)
Subjective Cure – no./total no. (%)‡	167/196 (85.2)	93/174 (53.4)	31.8 (22.6-40.3)	29.2 (20.5-37.4)
Objective Cure – no./total no. (%)§	140/183 (76.5)	94/160 (58.8)	17.8 (7.9-27.3)	15.5 (6.4-24.2)
			P Value ¶	
Change in UDI domain score‖				
Urinary incontinence	-37.3 ±20.9**	-26.9 ±20.6**	<0.001	<0.001
Overactive bladder	-15.5 ±20.5**	-10.6 ±19.5**	0.02	0.01
Obstructive micturition	-7.9 ±22.4**	-3.8 ±20.1**	0.06	0.06
Discomfort/pain	-7.4 ±13.8**	-5.4 ±11.6**	0.15	0.18
Genital prolapse	-1.8 ±11.6**	-1.9 ±10.8**	0.97	0.77
Change in IIQ Domain scores ‖ ††				
Physical functioning	-13.2 ±17.2	-10.3 ±17.0	0.11	0.12
Mobility	-24.6 ±19.9	-17.5 ±21.8	0.001	0.004
Emotional health	-15.1 ±15.7	-11.8 ±18.1	0.07	0.24
Social functioning	-8.5 ±16.6	-9.7 ±19.3	0.54	0.55
Embarrassment	-26.6 ±23.2	-19.3 ±24.5	0.004	0.006

* Plus-minus values are means ± SD. PGI-I denotes Patient Global Impression of Improvement.
† P≤ 0.001 for all four outcomes in the analyses of both the original data and the imputed data.
‡ Subjective cure was measured with the UDI question, "Do you experience urine leakage related to physical activity, coughing or sneezing?"
§ Objective cure was defined as a negative provocative cough stress test.
¶ P Values are for comparisons between the physiotherapy group and the surgery group.
‖ Data were available for 193 women in the surgery group and 171 women in the physiotherapy group.
** P<0.001 for the change in the domain score over time in the analyses of both the original data and the imputed data.
†† P<0.001 for changes in all domain scores over time for both groups in the analysis of both the original data and the imputed data.

Post Hoc Per-Protocol Analysis

Table 4 shows the results of the post hoc per protocol analysis comparing women who underwent only physiotherapy (103), those who underwent surgery after physiotherapy (99), and those who underwent initial surgery (215). At 12 months, the proportion of women who reported improvement was lower among women who underwent only physiotherapy than among women in the physiotherapy group who crossed over to the surgery group (absolute difference, 61.8 percentage points) or women who underwent initial surgery (absolute difference, 59.1 percentage points). Women who underwent only physiotherapy also had lower frequencies of subjective and objective cure, as compared with both groups of women who

Table 3. Adverse Events.*

Adverse Event	Physiotherapy Group (N = 202)†	Surgery Group (N = 215)
	no. of events (%)	
Serious adverse events		
Bladder perforation‡	0	6 (2.8)
Vaginal epithelial perforation	2(1.0)	8(3.7)
Reoperation for tape exposure	1 (0.5)	5 (2.3)
Reoperation to loosen tape	0	1 (0.5)
Postoperative bleeding	1(0.5)	0
Hematoma§	4 (2.0)	16 (7.4)
Blood loss >500cc	1(0.5)	2 (0.9)
New urge urinary incontinence	5 (2.5)	13 (6.0)

* Adverse events occurred in 41 women
† All adverse events in the physiotherapy group occurred in women who crossed over to the surgery group
‡ P=0.03.
§ P=0.01.

underwent surgery. Outcomes were similar between the women who underwent surgery after physiotherapy and those who underwent surgery initially. The mean number of physiotherapy sessions attended was 9.1±4.9 among women who did not cross over to the surgery group and 7.4±4.4 among women who did cross over (P = 0.06). When we considered the last PGI-I assessment for women who underwent physiotherapy alone and were lost to follow-up, we found that 76% of women (16 of 21) reported no improvement (**Supplementary Table 3**).

DISCUSSION

In this Dutch nationwide, multicentre trial, we compared strategies of initial surgery and initial physiotherapy, with an option to cross over to surgery, in the treatment of women with moderate- to- severe stress-predominant urinary incontinence. Women randomly assigned to undergo initial surgery were significantly more likely to have improvement at 12 months than were those assigned to receive initial physiotherapy. Surgery also resulted in greater improvement than did physiotherapy on all secondary end points. The benefits of surgery persisted in analyses involving multiple imputation of missing data. In a subsequent per-protocol analysis, women in the physiotherapy group who crossed over to the surgery group had outcomes that were similar to those among women who underwent initial surgery, whereas women who underwent only physiotherapy had significantly less favorable outcomes.

Our study has some limitations. Selection bias may have occurred. Women with a preference for surgery may have been more likely to participate in the study, because they otherwise would have received initial physiotherapy according to Dutch guidelines. In addition, women who had undergone physiotherapy more than 6 months before entering the trial were allowed to participate,

Table 4. Per-Protocol Analysis of Primary and Secondary Outcomes at 12 Months*

Outcome	Physio-therapy Only (N = 103)	Surgery after physio-therapy (N = 99)	Initial Surgery (N =215)	P value		
				Physiotherapy Only vs. Surgery after Physiotherapy	Surgery after Physiotherapy vs. Initial Surgery	Physiotherapy Only vs. Initial Surgery
PGI-I improvement – no./ total no (%)	26/82 (31.7)	86/92 (93.5)	177/195 (90.8)	<0.001	0.68	<0.001
PGI-S no symptoms – no./ total no. (%)	30/82 (36.6)	84/92 (91.3)	167/195 (85.6)	<0.001	1.00	<0.001
Subjective cure SUI – no./ total no. (%)	13/82 (15.9)	80/92 (87.0)	167/195 (85.2)	<0.001	1.00	<0.001
Objective cure SUI – no./ total no. (%)	33/75(44.0)	61/85 (71.8)	140/183 (76.5)	<0.001	1.00	<0.001
Physiotherapy sessions – no.	9.1±4.9	7.4±4.4	0.6±1.9	0.06	<0.001	<0.001
Change in UDI domain score						
Urinary Incontinence	-10.9 (20.8)	-41.3 (20.6)	-37.3 (20.9)	<0.001	0.42	<0.001
Overactive bladder	-6.4 (18.2)	-14.4 (19.9)	-15.5 (20.5)	0.03	1.00	0.002
Obstructive Micturition	-0.21 (20.3)	-7.0 (19.4)	-7.9 (22.4)	0.11	1.00	0.02
Discomfort or pain	-4.0 (10.4)	-6.7 (12.5)	-7.4 (13.8)	0.50	1.00	0.15
Genital prolapse	-1.3 (6.4)	-2.4 (13.5)	-1.8 (11.6)	1.00	1.00	1.00
Change in IIQ domain score						
Physical	-5.6 (13.0)	-14.5 (19.1)	-13.2 (17.2)	0.002	1.00	0.002
Mobility	-8.8 (18.9)	-25.4 (21.3)	-24.6 (19.9)	<0.001	1.00	<0.001
Emotional	-6.4 (16.2)	-16.7 (18.4)	-15.1 (15.7)	<0.001	1.00	<0.001
Social	-5.6 (14.7)	-13.3 (22.1)	-8.5 (16.6)	0.01	0.10	0.65
Embarrassment	-10.7 (18.4)	-27.1 (26.7)	-26.6 (23.2)	<0.001	1.00	<0.001

* Plus-minus values are means ±SD

although they represented only one fifth of the study population; a negative experience with prior physiotherapy may have negatively affected their adherence to the study regimen and the number of sessions they attended, which could have resulted in a lower efficacy of physiotherapy.[29] However, this possibility is not supported by our data; in the physiotherapy group, prior physiotherapy was similarly frequent among those who crossed over to surgery and those who did not.

The high crossover rate (49.0%) among women assigned to the physiotherapy group complicates the interpretation of results, because we used a modified intention-to-treat analysis. To address this problem, we performed a post hoc per-protocol analysis, which showed a favorable effect of additional surgery in the physiotherapy group.

Strengths of our study include our randomised design and inclusion of a variety of centers (24% of Dutch university and general hospitals), as well as many gynecologists, urologists, and certified

pelvic physiotherapists (17% of certified Dutch pelvic physiotherapists). Because we allowed both the transobturator and retropubic techniques for the placement of polypropylene tape, the range of typical clinical practice was represented in the surgery group. Complications of surgery were limited and were consistent with those seen in prior studies of sling surgery.[11,12] We used patient-reported outcomes because clinicians' assessments have often been shown to underestimate the degree of symptom-related distress perceived by women.30,31 In our study, both subjective and objective outcomes in the surgery group were superior to those in the physiotherapy group

The frequency of improvement in the surgery group (90.8%) was slightly higher than that reported in the literature (68 to 87%).[20-23,32-34] Heterogeneity in the study design, patient population, interventions, and outcome measures may account for this difference.[11] The improvement rate (64.4%) we observed in the physiotherapy group, which included women who crossed over to surgery, was higher than the rates in two other physiotherapy studies, which did not allow crossover (33% and 43%).[35,36] Our high crossover rate is the most likely explanation; the frequency of improvement among women who did not cross over to surgery (31.7%) is similar to the frequencies in the other studies.

In contrast to the findings in another prior study,[5] the rate of subjective cure among women in the physiotherapy group in our study was lower than the rate of objective cure (15.9% vs. 44.0%). It is possible that women who underwent physiotherapy were able to control their pelvic-floor muscles during the clinical provocative cough test yet still had stress urinary incontinence in everyday life in response to unexpected events.

In summary, the results of our trial show that women with moderate-to-severe stress urinary incontinence have significantly better subjective and objective outcomes at 12 months after surgery than after physiotherapy. Our findings suggest that women with this condition should be counseled regarding both pelvic-floor muscle training and midurethral-sling surgery as initial treatment options. Information on expected outcomes with both interventions, as well as on the potential, albeit infrequent, complications of surgery, will allow for individualised decision making by each woman and her health care provider.

REFERENCES

1. Novara G, Artibani W, Barber MD, et al. Updated systematic review and meta analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence. Eur Urol 2010; 58:218-38.
2. van der Vaart CH, de Leeuw JRJ, Roovers JPWR, et al. The effect of urinary incontinence and overactive bladder symptoms on quality of life in young women. BJU Int 2002; 90:544-9.
3. Coyne KS, Zhou Z, Thompson C, et al. The impact on health-related quality of life of stress, urge and mixed urinary incontinence. BJU Int 2003; 92:731-5.
4. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn 2010; 29:4-20.
5. Dumoulin C, Hay-Smith J. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev 2010; (1):CD005654.
6. Imamura M, Abrams P, Bain C, et al. Systematic review and economic modelling of the effectiveness and cost-effectiveness of non-surgical treatments for women with stress urinary incontinence. Health Technol Assess 2010; 14:1-188, iii-iv.
7. Cammu H, Van Nylen M, Blockeel C, et al. Who will benefit from pelvic floor muscle training for stress urinary incontinence? Am J Obstet Gynecol 2004; 191:1152-7.
8. Lamers BHC, Vaart CH van der. Medium-term efficacy of pelvic floor muscle training for female urinary incontinence in daily practice. Int Urogynecol J Pelvic Floor Dysfunct 2007; 18:301-7.
9. Bø K, Kvarstein B, Nygaard I. Lower urinary tract symptoms and pelvic floor muscle exercise adherence after 15 years. Obstet Gynecol 2005; 105:999-1005.
10. Ulmsten U, Henriksson L, Johnson P, et al. An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 1996; 7:81-5.
11. Ogah J, Cody JD, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev 2009; (4):CD006375.
12. Latthe PM, Singh P, Foon R, et al. Two routes of transobturator tape procedures in stress urinary incontinence: a meta-analysis with direct and indirect comparison of randomized trials. BJU Int 2010; 106:68-76.
13. Labrie J, van der Graaf Y, Buskens E, et al. Protocol for Physiotherapy Or TVT Randomised Efficacy Trial (PORTRET): a multicentre randomised controlled trial to assess the cost-effectiveness of the tension free vaginal tape versus pelvic floor muscle training in women with symptomatic moderate to severe stress urinary incontinence. BMC Womens Health 2009; 9:24.
14. Sandvik H, Hunskaar S, Seim A, et al. Validation of severity index in female urinary incontinence and its implementation in an epidemiological survey. J Epidemiol Community Health 1993; 47:497-9.
15. Nager CW, Brubaker L, Litman HJ, et al. A randomized trial of urodynamic testing before stress-incontinence surgery. N Engl J Med 2012; 366:1987-97.
16. de Leval J. Novel surgical technique for the treatment of female stress urinary incontinence: transobturator vaginal tape inside-out. Eur Urol 2003; 44:724-30.
17. Berghmans L, Bernards A, Bluyssen A, et al. KNGF-richtlijn Stress Urine-Incontinentie.
18. Ned Tijdschr Fysiother 2003; 115: Suppl 1:1-24. (In Dutch.)
19. Miller JM, Perucchini D, Carchidi LT, et al. Pelvic floor muscle contraction during a cough and decreased vesical neck mobility. Obstet Gynecol 2001; 97:255-60.
20. Yalcin I, Bump RC. Validation of two global impression questionnaires for incontinence. Am J Obstet Gynecol 2003; 189:98-101.
21. Padmanabhan P, Nitti VW. Female stress urinary incontinence: how do patient and physician perspectives correlate in assessment of outcomes? Curr Opin Urol 2006; 16:212-8.
22. Biggs GY, Ballert KN, Rosenblum N, et al. Patient-reported outcomes for tension-free vaginal tape-obturator in women treated with a previous anti-incontinence procedure. Int Urogynecol J Pelvic Floor Dysfunct 2009; 20:331-5.
23. Ballert KN, Rose AE, Biggs GY, et al. Outcomes of patients lost to follow-up after midurethral synthetic slings — successes or failures? J Urol 2010; 183:1455-8.
24. Abdel-Fattah M, Ramsay I, Pringle S, et al. Randomised prospective singleblinded study comparing 'inside-out' versus 'outside-in' transobturator tapes in the management of urodynamic stress incontinence 1-year outcomes from the E-TOT study. BJOG 2010; 117:870-8.

25. Shumaker SA, Wyman JF, Uebersax JS, et al. Health-related quality of life measures for women with urinary incontinence: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Qual Life Res 1994; 3: 291-306.
26. van der Vaart CH, de Leeuw JRJ, Roovers JPWR, et al. Measuring health-related quality of life in women with urogenital dysfunction: the Urogenital Distress Inventory and Incontinence Impact Questionnaire revisited. Neurourol Urodyn 2003; 22:97-104.
27. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009; 338: b2393.
28. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods.
29. Stat Med 1998; 17:873-90. [Erratum, Stat Med 1999;18:1293.]
30. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawence Erlbaum, 1988.
31. Dumoulin C, Glazener C, Jenkinson D. Determining the optimal pelvic floor muscle training regimen for women with stress urinary incontinence. Neurourol Urodyn 2011; 30:746-53.
32. Staskin DR, Kelleher C, Avery K, et al. Patient-reported outcome assessment. In: Abrams P, Cardozo L, Khoury S, Wein A, eds. Incontinence. 4th ed. Paris: Health Publication, 2009:363-412.
33. Black NA, Downs SH. The effectiveness of surgery for stress incontinence in women: a systematic review. Br J Urol 1996; 78:497-510.
34. Nilsson CG, Palva K, Rezapour M, et al. Eleven years prospective follow- up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2008; 19:1043-7.
35. Foglia G, Mistrangelo E, Lijoi D, et al. Transfascial vaginal tape (TFT): a simple, safe and cost-effective procedure for stress urinary incontinence: a preliminary study.
36. Arch Gynecol Obstet 2007; 276:59-63.
37. Jelovsek JE, Barber MD, Karram MM, et al. Randomised trial of laparoscopic Burch colposuspension versus tension-free vaginal tape: longterm follow-up. BJOG 2008; 115:219-25.
38. Richter HE, Burgio KL, Brubaker L, et al. Continence pessary compared with behavioral therapy or combined therapy for stress incontinence: a randomized controlled trial. Obstet Gynecol 2010; 115: 609-17.
39. Tannenbaum C, Brouillette J, Corcos J. Rating improvements in urinary incontinence: do patients and their physicians agree? Age Ageing 2008; 37:379-83.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Sandvik Index

Sandvik Index	Quantity of urine loss	
	1 = drops	2 = more than drops
Episodes		
1 = < 1 time a month	1	2
2 = 1 to more times a month	2	4
3 = 1 to more times a week	3	6
4 = daily	4	8

1-2 points; mild incontinence, 3-4 points; moderate incontinence, 6-8 points; severe incontinence

Supplementary Table 2. PGI-I and PGI-S at all follow-up moments

Outcome	Surgery Group (N = 215)	Physiotherapy Group (N = 202)	Treatment Effect percentage points (95% CI)
2 months			
PGI-I improved†	175/201 (87.1)	25/194 (12.9)	74.2 (67.5-80.8)
PGI-S no symptoms†	167/201 (83.1)	25/193 (13.0)	70.1 (63.1-77.2)
4 months			
PGI-I improved†	182/200 (91.0)	59/190 (31.1)	59.9 (52.3-67.6)
PGI-S no symptoms†	166/199 (83.4)	59/189 (31.2)	52.2 (43.8-60.6)
6 months			
PGI-I improved†	180/203 (88.7)	81/182 (44.5)	44.2 (35.7-52.7)
PGI-S no symptoms†	173/203 (85.2)	76/182 (41.8)	43.5 (34.7-52.2)
12 months			
PGI-I improved†	177/195 (90.8)	112/174 (64.4)	26.4 (18.1-34.5)
PGI-S no symptoms†	167/195 (85.6)	114/174 (65.5)	20.1 (11.4-28.6)
18 months			
PGI-I improved†	163/178 (91.6)	119/159 (74.8)	16.7 (8.8-24.7)
PGI-S no symptoms‡	152/177 (85.9)	117/159 (73.6)	12.3 (3.7-20.9)

PGI-I denotes Patient Global Impression of Improvement; PGI-S denotes Patient global impression of severity
Values are numbers of women/total (percentage)
† comparisons were significant at p≤ 0.001 ,
‡ comparison was significant at p=0.005
At 12 months follow-up (49%) 99/202 and at 18 months follow-up (61%) 123/202 underwent additional surgery after initial physiotherapy

Supplementary Table 3. Women lost to follow-up

Outcome	Physiotherapy Only (N = 21)	Surgery after Physiotherapy (N = 7)	Initial Surgery (N = 19)
Last measured PGI-I at:			
Never†	0	0	3
2 months	5	0	1
4 months	4	3	5
6 months	12	4	10
Last measured PGI-I			
No improvement	16 (76%)	4 (57%)	5 (26%)

PGI-I: Patient global impression of improvement
† PGI-I was not measured at baseline; these patients were loss to follow-up before the 2 months visit.


5

PREDICTING WHO WILL UNDERGO SURGERY AFTER PHYSIOTHERAPY FOR FEMALE STRESS URINARY INCONTINENCE

J. Labrie, A.L.M. Lagro-Janssen, K. Fischer, L.C.M. Berghmans, and C.H. van der Vaart
on behalf of the PORTRET study group

Int Urogynecol J 2014 ; Jul 29. [Epub ahead of print]

ABSTRACT

Introduction and hypothesis

To predict who will undergo midurethral slingsurgery (slingsurgery) after initial pelvic floor muscle training (physiotherapy) for stress urinary incontinence in women.

Methods

This was a cohort study including women with moderate to severe stress incontinence who were allocated to the physiotherapy arm from a previously reported multicentre trial comparing initial slingsurgery or initial physiotherapy in treating stress urinary incontinence. Crossover to slingsurgery was allowed.

Results

Data from 198/230 women who were randomised to physiotherapy was available for analysis, of whom 97/198 (49 %) crossed over to slingsurgery. Prognostic factors for undergoing slingsurgery after physiotherapy were age <55 years at baseline (OR 2.87; 95 % CI 1.30–6.32), higher educational level (OR 3.28; 95 % CI 0.80–13.47), severe incontinence at baseline according to the Sandvik index (OR 1.77; 95 % CI 0.95–3.29) and Urogenital Distress Inventory; incontinence domain score (OR 1.03; per point; 95 % CI 1.01–1.65). Furthermore, there was interaction between age <55 years and higher educational level (OR 0.09; 95 % CI 0.02–0.46). Using these variables we constructed a prediction rule to estimate the risk of slingsurgery after initial physiotherapy.

Conclusion

In women with moderate to severe stress incontinence, individual prediction for slingsurgery after initial physiotherapy is possible, thus enabling shared decision making for the choice between initial conservative or invasive management of stress urinary incontinence.

INTRODUCTION

The benefits of pelvic floor muscle training (physiotherapy) for urinary incontinence were first reported by Kegel in 1948.[1] Despite good results, this non-invasive approach was discarded and forgotten until the 1980s when physiotherapy was rediscovered. The Cochrane review on physiotherapy for urinary incontinence in women concluded that women who underwent physiotherapy were more likely to report cure or improvement than women who did not.[2] However, physiotherapy is not the definitive solution for all women with stress urinary incontinence (SUI): 5 % to 49 % of women treated for SUI will be objectively cured after physiotherapy compared to 57–92% of women treated with midurethral slingsurgery (slingsurgery).[3–5]

In our recently published randomised controlled trial, 49% of women with moderate to severe SUI initially treated with physiotherapy had proceeded to slingsurgery at 12 months' follow up.[6] Although many studies have reported on factors that might influence or predict the outcome of conservative therapy for SUI, little research has been performed on identifying women who will cross over to slingsurgery after initial physiotherapy. Factors reported in the literature that could negatively influence physiotherapy outcome are: severity of incontinence, number of incontinence episodes at start of treatment, poor outcome of previous physiotherapy, insufficient adherence to therapy, poor physical health, vaginal delivery, obesity, level of education, and age.[7–12]

The purpose of this study was to develop a prediction rule for the probability of crossover to slingsurgery after initial physiotherapy for SUI within 12 months' follow up.

METHODS

This cohort study was performed in women allocated to the physiotherapy arm of a multicentre pragmatic randomised trial comparing initial physiotherapy and initial slingsurgery for women with moderate to severe SUI.[13] The primary outcome for the original trial, i.e. improvement of incontinence at 12 months' follow up, was recently published.[6] Women who underwent previous anti-incontinence surgery or had concomitant pelvic organ prolapse were excluded. Women who underwent physiotherapy more than 6 months prior to randomisation were allowed to participate. Written informed consent was obtained from all participating women. Only data from women allocated to the initial physiotherapy arm of the original trial were used for the present analysis. The ethics committee of the University Medical Centre Utrecht (number: 07–278) and the institutional review boards at the individual participating sites approved the study protocol.

Interventions

For women in the physiotherapy arm in the original trial, daily clinical practice for The Netherlands was followed. Pelvic floor muscle training was performed, as recommended by the Dutch guidelines on SUI, by registered specialised pelvic physiotherapists only [14]. An initial number of nine sessions at 1-week or 2-week intervals in a maximum time of 6 months was advised. Use of biofeedback or electrostimulation was allowed. The training program incorporated close to maximum specific pelvic floor contractions, building up to three series of 8–12 contractions per

day, as part of strategies to functionally support the urethral closing mechanism. In case the treatment result was unsatisfactory and/or the physiotherapist agreed that the maximal effect was reached, women were allowed to discontinue physiotherapy and proceed to slingsurgery.

Baseline (demographic) characteristics of the physiotherapy group and surgical status at 12 months' follow up were used for this study. In the original protocol the prediction rule aimed to predict successful treatment of SUI. This endpoint was altered to crossover to slingsurgery at 12 months' follow up, because of the high crossover rate (49 %) to slingsurgery in our trial. The variables of interest for predicting crossover to slingsurgery were: age, educational level, parity, severity of incontinence at baseline (measured with the Sandvik index, Urogenital Distress Inventory (UDI) incontinence domain, and patient global impression of severity (PGI-S), body mass index, baseline pelvic floor function (contraction/relaxation) and previous physiotherapy[15–17]. In a deviation from the original study protocol, duration of symptoms and treatment modality were excluded whereas age and educational level were added to the variables of interest.

Statistical analyses

The association of variables of interest for crossing over to slingsurgery were first studied with univariate logistic regression. Possible interactions between variables were checked. Univariate odds ratios (OR) and regression coefficients (β) were calculated, with 95 % confidence intervals (CI) and P-values for determining significance. Variables with a P-value of 0.20 or less were entered in a multivariable regression model with a stepwise backward selection procedure to construct the prediction rule.

All variables were entered manually in a stepwise forward regression model to check accuracy. To reduce overfitting of the model, shrinkage of regression coefficients was performed according to the Heuristic formula of van Houwelingen et al. (model chi2-df/ model chi2=shrinkage factor).[18] From the final model each woman's predicted probability of slingsurgery within 12 months after starting physiotherapy was calculated with the following formula: Crossover to slingsurgery after physiotherapy= $1/[1+e-(\alpha+\beta1*X1+\beta2*X2... \beta k*Xk)]$ in which 'β' is the shrunk regression coefficient and X the variable in the regression model. A risk score was derived from the shrunk regression coefficients from the final multivariable regression model. All shrunk coefficients were divided by the smallest shrunk coefficient multiplied by 10 to calculate the risk score. Outcomes were rounded to the nearest integer.

Overall model discrimination was assessed by calculating the area under the receiver-operating curve. The agreement between predicted probabilities and the observed frequencies of slingsurgery after physiotherapy (calibration) was tested with the Hosmer-Lemeshow test. Based on the score distribution, arbitrary risk categories of women with low, intermediate, or high risks of slingsurgery were identified. Positive and negative predicted values were calculated for the different risk categories to facilitate clinical interpretation.

RESULTS

Between March 2008 and May 2010, a total of 230 women were randomised to physiotherapy. After randomisation, 27 women withdrew, did not start with physiotherapy, or did not wish to further participate, and one woman violated inclusion criteria. An additional four women with missing baseline values were excluded. Thus, the current analysis was based on 198/230 women. Within 12 months after start of physiotherapy, 97/198 (49 %) women crossed over to slingsurgery after discontinuation of initial physiotherapy. The mean time to crossover was 31.7±12.7 weeks. The mean number of physiotherapy sessions attended was 9.1±4.9 among women who did not cross over to the slingsurgery group and 7.4±4.4 for those who did cross over (P=0.06). Baseline characteristics for the 198 women randomised to initial physiotherapy are shown in **Table 1**.

Table 1. Baseline characteristics according to the need for slingsurgery within one year of physiotherapy*

Characteristic	Total (n=198)	Physiotherapy only (n=101)	Physiotherapy and Slingsurgery (n=97)
Age at baseline, years – mean ±SD	49.9±8.3	50.7±8.8	49.3±7.7
Educational level			
High school only	150(75.8)	70(69.3)	80(82.5)
ollege or University	48(24.2)	31(30.7)	17(18.5)
Parity –median (range)	2(0-7)	2(0-7)	2(0-5)
Body mass Index – mean ±SD	26.9±5.0	26.8±5.5	27.0±4.5
Postmenopausal	67(34.4)	35(35.4)	32(33.3)
Previous vaginal surgery	37(18.7)	20(19.8)	17(17.5)
Micturition /24hrs –median (range)	8(4-17)	8(4-14)	8(4-17)
Physiotherapy > 6 months before randomisation	38(20.1)	20(21.3)	18(18.9)
Pad use			
No pads	37(18.7)	20(19.8)	17 (17.5)
Daily ≤ 2 pads	68(34.3)	38(37.6)	30(30.9)
> 2 pads or diapers	93 (50.0)	43 (42.6)	50 (51.5)
Leakages/day– median (range)	3 (0-15)	2 (0-11)	3(0-15)
Sandvik Index, severe	116(58.6)	52(51.5)	64(66.0)
PGI-S, severe	32 (16.4)	9(9.0)	23(24.2)
UDI domains – mean ±SD			
Urinary Incontinence	41.1 ±19.2	36.4±17.1	45.9±20.1
Overactive Bladder	18.4 ±20.3	16.7±19.3	20.4±21.3
Obstructive Micturition	11.4 ±18.7	10.1±17.7	12.7±19.8
Pain/Discomfort	9.9 ±14.1	9.2±12.7	10.7±15.5
Prolapse	2.6 ±10.5	1.7±6.5	3.6±13.4

No.: number; PGIS; Patient Global Impression of Severity, UDI; Urogenital Distress Inventory, SD; Standard Deviation
*Values are numbers (%) unless stated differently.
Standard Deviation.

Prediction rule

All variables with P-values ≤0.20 in the univariate analyses were simultaneously entered in a multivariable regression model with a stepwise backward selection procedure to construct the prediction rule. Age was checked as a continuous variable and for different cut-off values in the univariable analysis. Regression coefficients were shrunk with a factor 0.681156.[18] The results of uni- and multivariable analysis are presented in **Table 2**.

Table 2. Result of univariable and multivariable analysis for slingsurgery after initial physiotherapy

Characteristic	Univariable analysis			Multivariable analysis			Score
	OR (95% CI)	P value	β	OR (95% CI)	P value	β	
Age ≤55 at baseline	1.53 (0.80-2.90)	0.20*	0.423	2.86 (1.30-6.32)	0.01	1.052	4
Higher Educational Level	0.51 (0.26-0.99)	0.05*	-0.677	3.28 (0.80-13.47)	0.10	1.187	4
Parity	1.29 (0.94-1.79)	0.12*	0.257				
Sandvik (severe)	1.66 (0.94-2.92)	0.08*	0.506	1.76 (0.95-3.29)	0.08	0.566	2
UDI Incontinence	1.03 (1.01-1.05)	0.001*	0.028	1.03 (1.01-1.05)	0.002	0.028	0.1
PGIS severe	3.37 (1.48-7.70)	0.004*	1.215				
Body-mass Index	1.01 (0.95-1.67)	0.81	0.007				
Baseline PFM contraction	0.97 (0.57-1.65)	0.91	-0.030				
Baseline PFM relaxation	0.81 (0.47-1.38)	0.43	-0.214				
Previous physiotherapy	0.92 (0.46-1.87)	0.82	-0.081				
HEL*Age≤55	0.40 (0.20-0.85)	0.02*	-0.910	0.09 (0.02-0.46)	0.004	-2.448	-9
Parity*Age≤55	1.31 (1.03-1.66)	0.03*	0.267				
HEL*Sandvik (severe)	0.62 (0.41-0.93)	0.02*	-0.481				
Constant				0.12	<0.001	-2.120	

PGIS; Patient Global Impression of Severity, UDI; Urogenital Distress Inventory, PFM; pelvic floor muscle, HEL; Higher Educational Level, *Entered in multivariable analysis

Risk scores were calculated by dividing all shrunk coefficients by the smallest shrunk coefficient multiplied by 10 (UDI incontinence domain, shrunken β=(10*0.028)/0.681156)). Eventually four variables and one interaction term associated with crossover to slingsurgery were used in the multivariable model: age ≤55 years, severe baseline incontinence complaints measured with the Sandvik index, severe complaints according to the PGI-S and higher educational level. Although higher educational level and age <55 years did not demonstrate a P-value<0.05 in the multivariable analysis, we did include these predictors in the prediction rule. This choice was made because the model including these predictors was the most accurate, with the highest area under the curve. Furthermore both predictors were shown to be significantly associated with outcome when used as interaction term.

The following prediction rule was constructed.

Risk score = (4*age < 55) + (2*Sandvik – severe) + (4*higher educational level) + (0.1*UDI – score on incontinence domain) + (– 9*(higher educational level*age < 55)).

Risk scores were calculated for 198 women. The calculated scores in our population ranged from 0 to 16, corresponding with a risk varying from 0.12 to 0.90. The predicted risk for crossing over to slingsurgery after physiotherapy before 12 months' follow up is shown in **Figure 1.** Women were divided into three arbitrary risk categories <5, 5–10 and >10 points based on score distribution. Scores <5 were seen in 17 % between 5 and 10 in 65 % and >10 in 18 % of women. In **Table 3.**, positive predictive values for the different risk categories are presented. The positive predictive value for slingsurgery after physiotherapy was 77 % (95 % CI 60–90) for women with a score of more than 10 points (35 of 198 women had a score >10 and 27/35 of these women had slingsurgery). The negative predictive value for women with a score <5 was 79 % (95 % CI 62–91) (34 of 198 had a score <5 and 27/34 did not undergo slingsurgery). Converting the logistic regression model to a risk score did not affect discrimination: both the final model and the risk-score demonstrated an area under the concentration-time curve (AUC) of 0.71; (95 % CI 0.64–0.79) The Hosmer–Lemeshow goodness-of-fit test-statistic indicated good calibration (P=0.88).

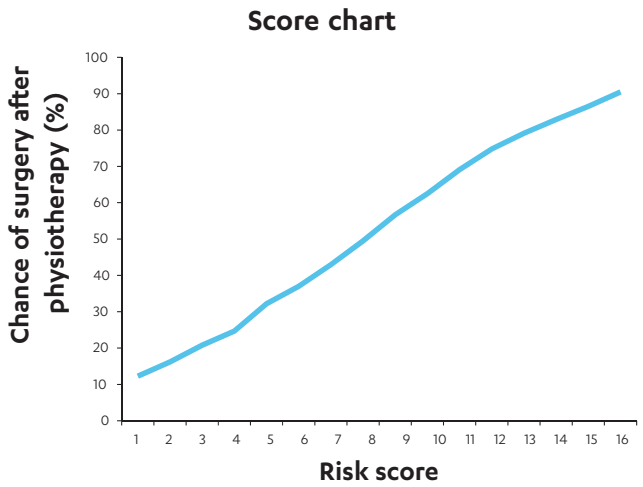


Figure 1. Risk score chart

DISCUSSION

We constructed a prediction rule to calculate the probability of crossover to slingsurgery after initial pelvic floor muscle training for moderate to severe stress urinary incontinence. In addition we constructed a risk score chart that enables individualised counselling. Independent predictors of crossover to slingsurgery after initial physiotherapy for SUI were: age <55 years, higher

Table 3. Risk categories with positive predictive values

Score*	No. of patients	Expected Nr with operation <12 months	No. of women with operation <12months FU	PPV
<5	34	7	7	0.21
5-10	129	64	64	0.50
>10	35	27	27	0.77

PPV; positive predictive value,
*Scores <5, 5-10 or >10 were considered as reference group for calculating the PPV.

educational level and more severe incontinence complaints before start of treatment according to the UDI incontinence domain (symptom bother) and the Sandvik index (symptom severity).

For correct interpretation of these findings, some aspects of study design need to be addressed. Selection bias may have occurred at inclusion in the original randomised trial. Women with a preference for slingsurgery may have been more likely to participate in our trial, because outside the trial initial physiotherapy was the standard treatment. Furthermore, women who underwent physiotherapy >6 months prior to inclusion were allowed to participate and this could have resulted in reduced success of physiotherapy due to lower motivation and/or compliance. However, this was not confirmed: previous physiotherapy was not associated with crossover to slingsurgery in the univariable analysis (**Table 2.**). Physiotherapy was performed by 83 specialised physiotherapists according to the Dutch national protocol, thus increasing external validity by broad representation of clinical practice.

In developing the prediction rule we deviated from the original protocol. The original protocol intended to use both arms of the trial to predict success after treatment. Because of the high crossover rate of 49 %, it was decided to use data from the physiotherapy group only. Therefore treatment modality could not be included as a possible predictor. Duration of symptoms, which was originally described as a possible predictor, could not be included because we were unable to collect complete and reliable data on the duration of symptoms. Two additional non-data driven predictors were added: age and educational level. These two variables have been associated with outcome of physiotherapy for SUI.[9,12,19,20] Although the statistical analysis as planned in the original protocol was altered, the newly included predictors were preselected based on literature, before any statistical analyses were undertaken.

Strengths of our study include the use of one arm of a randomised trial, providing us with a large group of women. Furthermore, the number of variables considered was restricted and due to the large number of women crossing over to slingsurgery the model was adequately powered.[21] Overfitting bias was reduced by excluding prognostic variables with a P-value >0.20[22,23]

Internal validation and correcting for overfitting by shrinking the regression coefficients was performed. However, external validation of the predicting rule and impact analyses has to be performed in a new cohort study since our population size was not large enough to both develop and validate the prediction rule.

Data on predictors for successful pelvic floor muscle training therapy for stress incontinence have been conflicting. Regarding the association between more severe complaints (at baseline)

and success of conservative management, Burgio et al.[9] performed a secondary analysis of three randomised clinical trials and reported that women who experienced more frequent episodes of incontinence (>10 per week) were less likely to be improved after conservative intervention (≥75 % reduction of incontinence episodes as recorded on bladder diary). In a prospective cohort study Hendriks et al. [10] demonstrated that severe SUI at baseline (PRAFAB-Q score≥14 points) was predictive of poor outcome of physiotherapy for SUI. In contrast, other studies could not demonstrate a relationship between severity of incontinence at baseline and outcome of conservative treatment [12,24]. Unfortunately these studies only presented short-term outcomes and lacked subjective measures for severity thus making comparisons difficult.

The relationship between higher educational level and lower success of conservative treatment was corroborated by Burgio et al.[9] In contrast, higher educational level was found to be predictive of successful conservative management of SUI with 2–3 months' follow up by Hendriks et al.[10] and Schaffer et al.[24] However, these studies presented short term results (2–3 months) and allowed women with concomitant prolapse to participate; furthermore, pessary therapy was included in the study by Schaffer et al.[24]

Literature on the association between age and outcome of conservative therapy is inconsistent. Some studies have reported better outcomes in younger women while others show no relationship between age and outcome of conservative management.[9,19,20,25] These studies mostly present short-term data in small groups, making comparison unreliable. Our prediction rule is a tool in providing individualised counselling for women with moderate to severe SUI on expected outcome of therapy. Using readily obtainable variables in our prediction rule, the physician will be able to present a chance of crossover to slingsurgery.

RECOMMENDATION AND CONCLUSION

In counselling for individualised treatment, information on chance of slingsurgery after physiotherapy should be combined with success rates and possible complications for both interventions. Women scoring <5 points could be counselled more towards initial physiotherapy whilst women scoring >10 points could be counselled more towards initial slingsurgery. However, most women scored in the intermediate risk group (5–10 points) with a 32–62 % chance of crossover. For these women personal preference after adequate counselling may play a more important role. In defining risk categories, based on our prediction rule, lies the power to enable patient-centred care, with shared decision-making and ensuring optimised individualised care.

Although the present model was corrected for overestimation, external validation is mandatory for full acceptance. Use of this rule will then further improve insight into the most appropriate initial treatment strategy for women with moderate to severe SUI. As was advised after the analysis of our original data, women should be able to choose either physiotherapy or slingsurgery as initial treatment for SUI after adequate counselling.[6]

REFERENCES

1. Kegel A Progressive resistance exercise in the functional restoration of the perineal muscles. Am J Obstet Gynecol 1948; 56:238–249
2. Dumoulin C, Hay-Smith J Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev 2010; (1):CD005654
3. Imamura M, Abrams P, Bain C, et al. Systematic review and economic modelling of the effectiveness and cost-effectiveness stress urinary incontinence. Health Technol Assess 2010; 14(40):1–506
4. Ogah J, Cody J, Rogerson L Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev 2010; (1):CD006375
5. Novara G, Artibani W, Barber MD, et al. Updated systematic review and meta-analysis
6. of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary. Eur Urol 2010; 58(2):218–238
7. Labrie J, Berghmans LCM, Fischer K, Milani AL, van der Wijk I, Smalbraak DJC et al Surgery versus physiotherapy for stress urinary incontinence. N Engl J Med 2013; 369(12):1124–1133
8. Cammu H, Van Nylen M, Blockeel C, et al. Who will benefit from pelvic floor muscle training for stress urinary incontinence? Am J Obstet Gynecol 2014; 191(4):1152–1157
9. Bø K, Kvarstein B, Nygaard I Lower urinary tract symptoms and pelvic floor muscle exercise adherence after 15 years. Obstet Gynecol 2005; 105(5 Pt 1):999–1005
10. Burgio K, Goode PS, Locher JL, et al. Predictors of outcome in the behavioral treatment of urinary incontinence in women. Obstet Gynecol 2003; 102(5):940–947
11. Hendriks EJM, Kessels AGH, Vet HCWD, et al. Prognostic indicators of poor short-term outcome of physiotherapy intervention in women with stress urinary incontinence. Neurourol Urodyn 2010; 343:336–343
12. Truijen G, Wyndaele JJ, Weyler J Conservative treatment of stress urinary incontinence in women: who will benefit? Int Urogynecol J Pelvic Floor Dysfunct 2001; 12(6):386–390
13. Theofrastous JP, Wyman JF, Bump RC, et al. Effects of pelvic floor muscle training on
14. strength and predictors of response in the treatment of urinary incontinence. Neurourol Urodyn 2002; 21(5):486–490
15. Labrie J, van der Graaf Y, Buskens E, et al. Protocol for Physiotherapy Or TVT Randomised Efficacy Trial (PORTRET): a multicentre randomised controlled trial to assess the cost-effectiveness of the tension free vaginal tape versus pelvic floor muscle training in women with symptomatic moderate to se. BMC Women's Health 2009; 9(24)
16. Bernards ATM, Berghmans LCM, Van Heeswijk-Faase IC, et al, KNGF-richtlijn Stress Urine-Incontinentie. Ned Tjjdschr Fysiother. 2011: Jaargang 121 Nr 3, Supplement
17. Sandvik H, Hunskaar S, Seim A, et al. Validation of incontinence severity index in female urinary implementation in an epidemiological survey. Management 1993; 497–9
18. Vaart CH van der, de Leeuw JRJ, Roovers JPWR, et al. Measuring health-related quality of life in women with urogenital dysfunction: the urogenital distress inventory and incontinence Impact questionnaire revisited. Neurourol Urodyn 2003; 22(2):97–104
19. Yalcin I, Bump R Validation of two global impression questionnaires for incontinence. Am J Obstet Gynecol 2003; 189(1):98–101
20. Houwelingen JC van, Le Cessie S Predictive value of statistical models. Stat Med 1990; 9:1303–1325
21. Weinberger MW, Goodman BM, Carnes M Long-term efficacy of nonsurgical urinary incontinence treatment in elderly women. J Gerontol A Biol Sci Med Sci 1999; 54(3):117–121
22. Schaffer J, Nager CW, Xiang F, et al. Predictors of success and satisfaction of nonsurgical therapy for stress urinary incontinence. Obstet Gynecol 2012; 120(1):91–97
23. Haynes RB, Sackett DL, Guyatt GH, et al. Clinical epidemiology: how to do clinical practice research, 2006; 3rd edn. Lippincott Williams & Wilkins, Philadelphia
24. Steyerberg EW, Eijkemans MJ, Harrell FE Jr, et al. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. Stat Med 2000; 19: 1059–1079
25. Steyerberg EW, Eijkemans MJ, Van Houwelingen JC, et al. Prognostic models based on literature and individual patient data in logistic regression analysis. Stat Med 2000; 19: 141–160
26. Subak LL, Quesenberry CP, Posner SF, et al. The effect of behavioral therapy on urinary incontinence: a randomized controlled trial. Obstet Gynecol 2002; 100:72–78

27. Smith DB, Boileau MA, Buan LD A self-directed home biofeedback system for women with symptoms of stress, urge, and mixed incontinence. S J Wound Ostomy Continence Nurs 2000; 27(4): 240–246


6

COST-UTILITY ANALYSIS OF SURGERY VERSUS PHYSIOTHERAPY FOR STRESS URINARY INCONTINENCE

J. Labrie, K. Fischer, L.C.M. Berghmans, A.L.M. Lagro-Janssen and C.H. van der Vaart
on behalf of the PORTRET study group

Submitted for publication

ABSTRACT

Background

The current international advice that all women with stress urinary incontinence should first undergo pelvic floor muscle training before midurethral slingsurgery is under debate. A direct comparison of costs between the two strategies could help in the decision for initial treatment strategies for stress urinary incontinence.

Objective

To perform an incremental cost-utility analysis of initial midurethral slingsurgery versus initial pelvic floor muscle training for stress urinary incontinence.

Design, Setting, Participants

A cost utility analysis was performed with data from a previously reported multicentre randomised controlled trial.

Outcome measurement and statistical analysis

Crossover between groups was allowed and data were analysed following the intention to treat principle. Treatment costs were derived from questionnaires at baseline 2, 4, 6, and 12 months follow-up. Quality of life was measured with the EuroQol questionnaire and the incremental cost per quality adjusted life years i.e. incremental cost-effectiveness ratio (ICER) was calculated.

Results

In total; 49% of women crossed over to slingsurgery and 11% of women crossed over to physiotherapy. The incremental cost for initial slingsurgery was €1091 (95% CI; 566-1617). The mean ICER for initial slingsurgery was € 54.377 with a 74% probability of the ICER remaining below the Dutch threshold of €80.000 per QALY gained.

Conclusion

Initial midurethral slingsurgery is a cost effective treatment approach compared to initial pelvic floor muscle training for moderate to severe urinary stress incontinent women. From a cost perspective both options should be considered as initial treatment approach for SUI.

INTRODUCTION

Midurethral slingsurgery (slingsurgery) and Pelvic Floor Muscle Training (physiotherapy) are the two most commonly applied therapies for Stress Urinary Incontinence (SUI) in women. Currently, physiotherapy is advised to be initial treatment.[1] We previously reported a randomised controlled trial comparing slingsurgery versus physiotherapy for initial treatment of moderate to severe stress urinary incontinence in women.[2,3] After one year follow-up, slingsurgery as initial treatment was significantly more effective than physiotherapy in terms of objective and subjective cure as well as improvement of symptoms. [3]

In addition to clinical effectiveness, the costs of different treatment approaches should be considered in defining an initial treatment strategy for stress urinary incontinence. In other words, can we justify initial slingsurgery from a cost perspective point of view? Our study incorporated the collection of data regarding costs as secondary outcome measures. The objective of this paper is to present the incremental cost-utility analysis of initial treatment strategies for SUI, being either initial slingsurgery or initial physiotherapy.

METHODS

The randomised trial compared initial slingsurgery and initial physiotherapy for SUI, and recruited women in 23 (24%) hospitals in the Netherlands. Women aged 35 to 80 years with moderate to severe SUI without concomitant prolapse were included between March 2008 and May 2010. After written informed consent was obtained, women were allocated 1:1 to midurethral slingsurgery or pelvic floor muscle training as initial treatment. Blinding for randomisation outcome was not performed. The study protocol with in- and exclusion criteria and the main outcomes of the trial have been published previously.[2,3]

Economic Evaluation

An incremental cost-effectiveness analysis from a 1-year societal perspective was conducted. Incremental cost-effectiveness is defined as the difference in average costs per patient between the trial arms, divided by the difference in quality adjusted life years (QALY) over one year, i.e. the incremental cost per QALY gained per patient.

Data were collected at baseline and at two, four, six and 12 months follow-up. Costs were derived from a questionnaire containing items on; visits to the general practitioner and/or physiotherapist, distance travelled, time spent travelling, additional medical visits, normal working hours, time lost from work due to treatment for incontinence, incontinence pad use, operation and type of operation.

Direct medical costs

Direct medical costs encompassed costs related to the all-inclusive tariff of the "diagnosis treatment combinations" (DBCs) regarding surgical treatment or conservative management of SUI. Additional costs considered were: physiotherapy visits, additional general practitioner

and hospital visits and reimbursed sanitary pads. The Dutch all-inclusive tariff of the DBC is a lump sum tariff based on average treatment costs for a specific diagnosis. Each combination of a diagnosis and treatment has a build up of fixed elements with a specific partitioning (the DBC), which is stipulated by the Dutch Ministry of Health. The actual prices of a DBC can vary between hospitals; therefore the average DBC prices across participating hospitals were calculated for our analysis. For example, the DBCs (surgical treatment and conservative management) for treating urinary incontinence include costs for: visits to the outpatient clinic, diagnostic costs, surgery costs, imaging, clinical diagnostic blood testing, microbiology and pathology. Details on the components of DBCs for both treatment strategies evaluated are provided in **supplementary Table 1**.

Direct medical costs not included in the DBCs were calculated for each patient according to the tariff of 2010 in Euros.[4] For women who crossed over between treatment arms, both the DBCs for surgical and conservative management of SUI were included in the direct medical costs.

Indirect medical costs

Indirect medical costs included travel costs to the general practitioner, physiotherapist and hospital, use of non-reimbursed sanitary pads and costs related to absence from work. The costs for absence from work were calculated by multiplying the number of hours lost from work by the average Dutch hourly wages for women according to age.[4] Costs were calculated for each observational period and then added to obtain 1-year indirect medical costs.

Utility

We used a generic health related quality of life questionnaire, the Euroqol 5 D (EQ-5D), to measure health related quality of life at baseline, two, four, six and 12 months follow-up.[5] The EQ-5D questionnaire consists of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety or depression. A utility value according to the Dutch tariff has been derived from these five dimensions, with scores ranging from -0,3 (worst perceived health status) to 1 (perfect health status).[5,6]

Utility is multiplied by time to calculate quality adjusted life years (QALYs). For the present analysis, a weighted average for available utilities measured throughout the 12 months follow-up was calculated. Missing data were imputed as means when intermediate data were missing, or using last observation carried forward when women were lost to follow-up.

Cost utility analysis

The incremental cost-effectiveness ratio (ICER) was computed by dividing the incremental cost for the first year after randomisation by the incremental QALY for the initial slingsurgery group versus the initial physiotherapy group.

$$\text{ICER} = \frac{\text{COST initial slingsurgery - COST initial physiotherapy}}{\text{QALY initial slingsurgery - QALY initial physiotherapy}}$$

To evaluate uncertainty in the incremental cost outcomes, bootstrapping procedures were performed.[7] In bootstrap simulation, cost and effectiveness pairs are randomly drawn from the data to obtain samples equal in size to the original study sample to get new estimates of the incremental costs and effects.

The results of 1000 bootstrap procedures were used to draw a cost-effectiveness plane. The plane provides information directly interpretable as the probability of one treatment strategy being cost-effective compared to the alternative.

A sensitivity analysis was performed to explore the effects of crossover rates on cost-effectiveness. The outcomes of crossover rates varying from 0 to 100% crossover to slingsurgery were bootstrapped and cost-effectiveness planes were drawn to calculate the probability of cost-effectiveness.

Data were analysed following the intention to treat principle, using SPPS version 19.0 (SPSS Inc. Chicago, IL, USA). The cost-effectiveness plane was made with Excel version 14.3.9 (Microsoft Inc. Redmond, WA, USA) Student's T-test was used to compare continuous data between groups and differences for categorical data were compared with Fisher's exact test. Neither costs nor effects were discounted, as the time horizon of the analyses was limited to one year.

RESULTS

A total of 460 women gave informed consent to participate in the trial. Women were randomised to initial slingsurgery (230) or initial physiotherapy (230). In the slingsurgery group 15 women did not start treatment versus 28 in the physiotherapy group. For an additional 7 women in the physiotherapy group no data on costs or utilities was available. Hence, data for cost-analysis were available for 215 (93.5%) women in the slingsurgery group and 195 (84.8%) women in the physiotherapy group. A flowchart of the trial has previously been published.[3] In the physiotherapy group, 99 women underwent additional slingsurgery within 12 months follow-up and 22 women received additional physiotherapy after slingsurgery.

Table 1. Baseline characteristics

Characteristic	Slingsurgery Group (n=215)	Physiotherapy Group (n=202)
Age – yr	50.2±9.8	50.0±8.2
Educational level		
College or University – no./total no. (%)	56/211 (26.5)	49/199 (24.6)
Parity– median (range)	2 (0-4)	2 (0-7)
Body-mass Index– mean	26.4 ±5.0	26.9 ±5.0
Postmenopausal – no./total no. (%)	78/209 (37.3)	67/196 (34.2)
Paid employment – no./total no. (%)†	139/205 (67.8)	158/198 (79.8)
PGI-S severe complaints – no./total no. (%)	46/213 (21.5)	33/196 (16.8)
EQ-5D	0.901±0.134	±0.880±0.157

† $p<0.05$
± standard deviation

Study groups were similar at baseline (**Table 1.**) The groups had similar incontinence symptoms measured with the Urogenital Distress Inventory or HRQoL measured with the Incontinence Impact Questionnaire and EQ-5D. However, more women in the initial physiotherapy group (79.8%) had paid employment compared to women in the initial slingsurgery group (67.8%) (P<0.05).

Costs

The prices used to calculate costs are shown in **Table 2**. The average direct medical costs were higher for the initial slingsurgery group (€3124±886) versus the initial physiotherapy group (€2266 ±1701) P <0.001. (**Table 3**) Indirect medical costs were similar between groups (1163±1698) and (929±2334) respectively P=0.24. (**Table 3**) During the 12 months follow-up, average total costs in the initial slingsurgery group were €4287 (±SD 1906) per patient compared to €3195 (±SD 3255) for the initial physiotherapy group. (P<0.001, Incremental cost €1091 (95% CI; 566-1617).

Utilities

Utilities derived from the EuroQol questionnaire according to time and intervention are shown in **Figure 1.** In both groups the mean EQ-5D utility scores improved significantly during 12 months follow-up. At 2 and 4 months follow-up women in the initial slngsurgery group had significantly better outcomes on the in EQ-5D utility score. At 6 and 12 months follow-up, EQ-5D scores were similar for both groups. At one-year follow-up, the initial slingsurgery group showed a mean increase in utility of 0.06 (95% CI; 0.04-0.07, P<0.001) compared to an increase of 0.07 (95% CI; 0.05-0.10, P<0.001) in the initial physiotherapy group.

The weighted average for utility (QALY) at 12 months was only slightly higher for the slingsurgery group at 0.948±0.088 for women undergoing initial slingsurgery and 0.928±0.092 for women starting initial physiotherapy, with a difference of -0.020 (95% CI; 0.005-0.035) P=0.24.

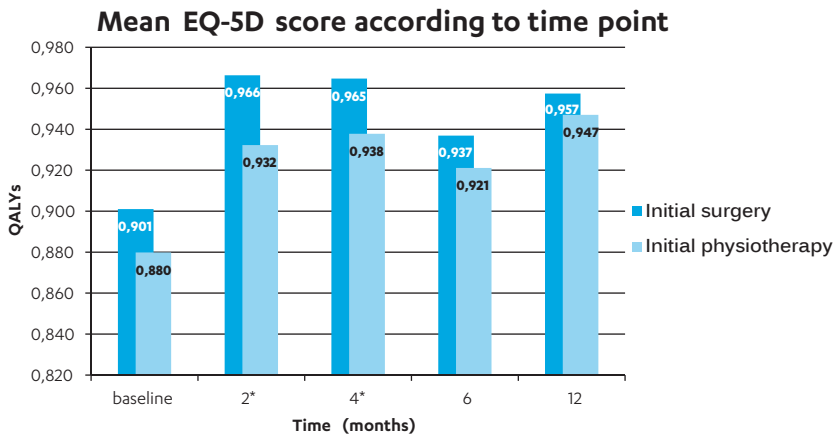


Figure 1. EQ-5D scor.
*P<0.05

Table 2. Prices used in cost analysis

Costs	Price per unit (€)
Direct Medical Costs	
DBC; Lumpsum slingsurgery in daycare	
University hospital	2378
General hospital	2379
DBC; Lumpsum slingsurgery >1 overnight stay	
University hospital	4822
General hospital	4547
DBC; Lumpsum consultation for incontinence	
University hospital	296
General hospital	265
Visit to physiotherapist	35
Visit to general practitioner	28
Extra hospital visit	
University hospital	129
General hospital	64
Refunded pads	
Incontinence pad	0.226
Incontinence pants	0.743
Indirect Medical Costs	
Travel per kilometre	0.20
Hours lost from work for women (2010)	
Age 30-35	27.54
Age 35-40	29.25
Age 40-45	29.06
Age 45-50	28.91
Age 50-55	29.25
Age 55-60	29.50
Age 60-65	28.67
Non refunded pads	
Inlay	0.022
Sanitary	0.083

DBC: diagnose treatment combination

Cost-effectiveness analysis

After bootstrap simulation the joint distribution of incremental cost and health effects was plotted in a cost-effectiveness plane (**Figure 2**). Midurethral slingsurgery was more effective in 99% of the bootstrap procedures (Northeast quadrant). The mean incremental cost-

Table 3. Mean costs at 12 months follow-up

Characteristic	Slingurgery Group (n=215)	Physiotherapy Group (n=202)	Δ (95% CI)	P Value
Direct medical costs	3124±886	2266±1701	858 (590-1126)	<0.001
DBC†	2909±714	1744±1616	1165 (918-1412)	<0.001
Physiotherapy visits‡	20±66	263±178	243 (216-269)	<0.001
Additional visit to GP	20±70	10±35		0.06
Additional visit to hospital	160±225	186±241	26 (19-72)	0.25
Sanitary pads refunded	15±39	63±85	48 (35-61)	<0.001
Indirect medical costs	1163±1698	929±2334	233 (-160-626)	0.24
Travel	25±39	49±60	24 (15-34)	<0.001
Time lost from work	1135±1607	874±2323	260 (-131-652)	0.20
Sanitary pads non refunded	3±7	6±11	3 (2-5)	<0.001
Total costs	4287±1906	3195±3255	1091 (566-1617)	<0.001

Plus-minus values are means ± SD; DBC denotes diagnosis treatment combination, GP: General practitioner
† Mean diagnose-treatment-combination price per patient.
‡ Visits to the physiotherapist are not incorporated in the DBC of conservative treatment

effectiveness utility ratio was € 54.377 with a 74% probability of the ICER remaining below the Dutch threshold of €80.000 per QALY gained. The probabilities of cost-effectiveness for different thresholds are shown in **supplementary Table 2.**

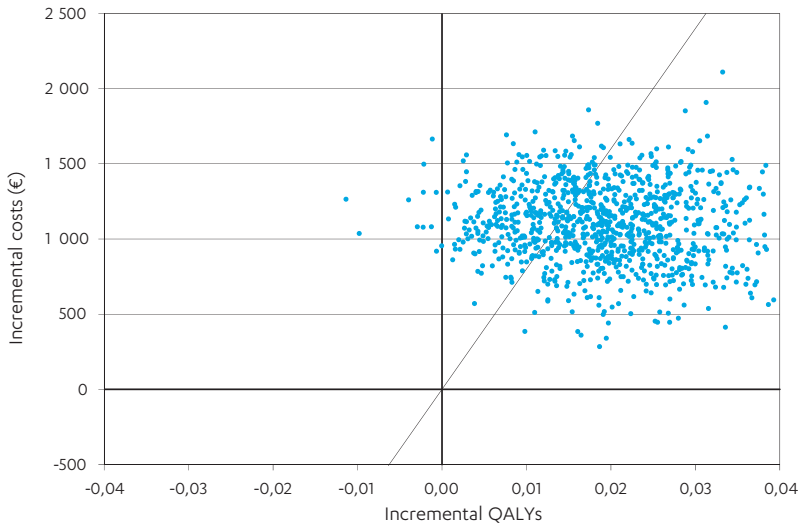


Figure 2. Cost-effectiveness plane.
Points represent the incremental cost per QALY for each of the 1000 repetition of the bootstrap procedure. Right from the Y-axis: Slingurgery is more effective. Above X-axis: higher costs for slingsurgery. 74% of bootstraps are under the cost acceptability line set at €80,000

Sensitivity analysis.

Because slingsurgery is more expensive than physiotherapy by definition, and the crossover from initial physiotherapy to slingsurgery was considerable, stability of our results was examined by analysing the effects of varying crossover rates. In **Table 4** the differences in costs are presented for crossover rates ranging from 0 to 100%. Incremental utility between groups remained stable across varying crossover rates. A crossover rate of 40% in the first year after start of physiotherapy resulted in an ICER of €76.784 with a 54% of bootstrap simulations under the Dutch cost-acceptability threshold set at €80.000, but <1% under the British threshold set at €35.400 (£30.000). When the crossover rate was changed to 60% an ICER of €33.327 was calculated with a 92% probability of the ICER remaining under the Dutch cost acceptability threshold and 54% under the British threshold.

Table 4. Sensitivity analysis of the ICER of initial slingsurgery over initial physiotherapy according to varying rates of cross-over from physiotherapy to slingsurgery and two cost acceptability thresholds

Crossover rate (%)	Δ Cost (€) (95%;[CI])	Δ QALY gain (95%;[CI])	ICER (€)	% under cost acceptability threshold €80.000	% under cost acceptability threshold £30.000 †
0	3,282 (2920 - 3616)	0.0201 (-0.002 - 0.043)	163.264	4%	0.00%
30	1974 (1644 - 2282)	0.020 (0.003 - 0.037)	98.565	30%	0.03%
40	1538 (1184 - 1867)	0.020 (0.004 - 0.036)	76.784	53%	0.8%
49 (Observed)	1091 (566 - 1617)	0.020 (0.005 - 0.035)	54.377	74%	14%
50	1102 (703 - 1465)	0.020 (0.005 - 0.035)	55.074	77%	13%
60	667 (214 - 1074)	0.020 (0.005 - 0.035)	33.327	92%	54%
100	-1,077 (-1784- -443)	0.0199 (0.000 - 0.041)	-54.027	99.79%	99.99%

CI; Confidence Interval

† €35400 calculated with the mean exchange rate for 2010,

DISCUSSION

Compared to initial physiotherapy for stress urinary incontinence, initial slingsurgery will cost €54.377 per QALY gained. Based on the general cost-acceptability threshold of €80.000 in the Netherlands we demonstrated that initial midurethral slingsurgery is cost-effective from a societal perspective at 12 months follow-up. Together with our previously published trial and prediction model this cost-utility analysis justifies a change in the paradigm that all women with SUI should undergo initial physiotherapy before undergoing slingsurgery for SUI.

Interpretation of our results is challenging because of the high crossover to slingsurgery (49%) in the physiotherapy group. By choosing to perform an intention to treat analysis we followed clinical daily practice in the Netherlands. In interpreting the outcomes it is important to keep in mind that we compared treatment strategies rather than isolated treatments.

A strength of our study is that we used a randomised design to calculate the cost-utility, avoiding the bias inherent to observational studies. Data were collected prospectively, based

on known expenditures or actual measurements. All questionnaires we used are validated and recommended by the International Continence Society and by the National Institute for Health and Clinical Excellence (NICE). A generic questionnaire (EQ-5D) for the measurement of QALYs was used, which may lack responsiveness in incontinence.[8-12] This could explain the small differences we observed in EQ-5D scores that were just under the minimally important difference of 0.074 as reported by Walters et al. in 2005.[13] In addition, baseline EQ-5D scores were quite high, which leave little opportunity for improvement.

Although results of initial slingsurgery were superior in the original trial, QALYs at 12 months follow-up were similar between the two groups; this may be attributed to the high crossover rate. The mean time of crossover from physiotherapy to slingsurgery was 31.7±12.7 weeks. This explains the observation that a significant difference between groups was only demonstrated at 2 and 4 months follow-up in EQ-5D scores. During this period the crossover rate was still low. The incontinence complaints of women who were operated on after physiotherapy improved directly upon slingsurgery, resulting in better EQ-5D scores and smaller differences between groups at 6 and 12 months follow-up.

A disease specific questionnaire for measuring QALYs could be the solution for a more sensitive measurement of incontinence related QALYs. In a recent study Albers-Heitner et al. used such a questionnaire (the International Consultation on Incontinence Questionnaire Short Form) to calculate a derivative from QALYs.[14] They calculated Incontinence Severity weighted Life Year (ISLY). This measure could be more sensitive to improvement, however interpretation of the costs per ISLY is impossible and results can not be compared to other conditions. Furthermore a conversion from the IIQ, which we used in our trial, to ISLY has not yet been published or validated. This could be very useful in future incontinence research.

The use of the Dutch DBC (lump sum) system for calculating treatment costs is another point of discussion. The DBC elements are established by the Dutch ministry of health and are a reflection of costs of the Dutch healthcare system. The build-up of the DBC is fixed but prices may vary between hospitals. By calculating an average for all participating hospitals (24% of Dutch hospitals) the DBC prices used in our study are a good reflection of the actual costs in the Netherlands. By providing the specific elements used to determine the built up of DBC prices, costs can be calculated for other healthcare systems.

Other cost effectiveness studies of slingsurgery[15-18] or pelvic floor muscle training [14,19] have been reported. Comparisons are difficult because these studies used different questionnaires for calculating QALYs, the duration of follow-up was short, and none directly compared slingsurgery to pelvic floor muscle training in a randomised study. Furthermore, the present study compared treatment strategies rather than specific treatments. Improvement in the initial physiotherapy group is partly due to the high crossover rate to slingsurgery.

In the sensitivity analysis we demonstrated that changing the crossover rate has a strong effect on the cost-effectiveness. Higher crossover rates resulted in higher cost-effectiveness for the initial slingsurgery group. The small effects of crossover on incremental utilities may explain why the cost-effectiveness of initial slingsurgery is mainly dependent on the crossover rate after one year. This furthermore justifies the choice for initial slingsurgery in the correctly selected women as was described in our previously published prediction model.[20]

CONCLUSION

Based on the current cost utility analysis, the strategy of initial midurethral slingsurgery is cost-effective compared to initial pelvic floor muscle training. Initial slingsurgery provides better outcomes at an acceptable incremental cost utility of € 54.377 which is below the commonly applied Dutch threshold of €80.000. Offering initial physiotherapy to all stress incontinent women leads to higher treatment costs if crossover is taken in account, whereas an individualised treatment approach is expected to be more cost-effective. Our previous recommendation that both treatment options should be considered as initial treatment for stress urinary incontinence based on differences in clinical outcome is now also justified from a cost perspective point of view.

REFERENCES

1. Dumoulin C, Hay-Smith EJC. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane database of systematic reviews 2010; Jan 20;(1);(1):CD005654.
2. Labrie J, van der Graaf Y, Buskens E, et al. Protocol for Physiotherapy Or TVT Randomised Efficacy Trial (PORTRET): a multicentre randomised controlled trial to assess the cost-effectiveness of the tension free vaginal tape versus pelvic floor muscle training in women with symptomatic moderate to se. BMC women's health 2009; 9(24).
3. Labrie J, Berghmans LCM, Fischer K, et al. Surgery versus Physiotherapy for Stress Urinary Incontinence N Engl J Med 2013; 369;12: 1124-33
4. Hakkaart-van Roijen L, Tan SS, Bouwmans, CAM. Handleiding voor kostenonderzoek methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg, geactualiseerde versie 2010, http://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/overige-publicaties/1007-handleiding-voor-kostenonderzoek/Handleiding+voor+kostenonderzoek.pdf
5. The EuroQol Group. EuroQol—A new facility for the measurement of health related quality of life. Health Policy 1990; 16:199–208.
6. Lamers LM, McDonnell J, Stalmeier PFM, et al. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. Health Econ. 2006; 15: 1121–1132
7. Efron B, Tibshirani R. An introduction to the bootstrap. London: Chapman and Hall; 1993
8. Imamura M, Abrams P, Bain C, et al. Systematic review and economic modelling of the effectiveness and cost-effectiveness of non-surgical treatments for women with stress urinary incontinence. Health Technol Assess. 2010; 14(40):1-188, iii-iv.
9. Innerkofler PC, Guenther V, Rehder P, et al. Improvement of quality of life, anxiety and depression after surgery in patients with stress urinary incontinence: results of a longitudinal short term follow-up. Health Qual Life Outcomes 2008; 6:72
10. Oh SJ, Ku JH. Is a generic quality of life instrument helpful for evaluating women with urinary incontinence? Qual Life Res 2006; 15:493 501.
11. Haywood KL, Garratt AM, Lall R, et al. EuroQol EQ-5D and condition specific measures of health outcome in women with urinary incontinence: reliability, validity and responsiveness. Qual Life Res 2008; 17:475 483.
12. Brazier J, Czoski-Murray C, Roberts J, et al. Estimation of a Preference based index from a condition'specific measure: the King's Health Questionnaire. Med Decis Making 2008; 28:113 126
13. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res. 2005; 14(6):1523-32.
14. Albers-Heitner CP, Joore MA, Winkens RAG, et al. Cost-Effectiveness of Involving Nurse Specialists for Adult Patients With Urinary Incontinence in Primary Care Compared to Care-as-Usual: An Economic Evaluation Alongside a Pragmatic randomized Controlled Trial; Neurourology and Urodynamics 2012; 31:526–534
15. Lier D, Ross S, Tang S, et al. Trans obturator tape compared with tension free vaginal tape in the surgical treatment of stress urinary incontinence: a cost utility analysis. BJOG 2011;118:550 556.
16. Boyers D, Kilonzo M, Mostafa A, et al. "Adjustable Anchored Single Incision Mini Slings (SIMS Ajust) compared to Standard Midurethral Slings (SMUS), Tension free Vaginal Tapes (TVT O); "A health economic evaluation". BJU Int 2013; 112:1169 1177.
17. Manca A, Sculphera MJ, Ward K, et al. A cost–utility analysis of tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence. BJOG 2003; Vol. 110, pp. 255–262
18. Seklehner S, Laudano MA, Te AE, et al. A cost-effectiveness analysis of retropubic midurethral sling versus transobturator midurethral sling for female stress urinary incontinence. Neurourol Urodyn. 2013; 14. [Epub ahead of print]
19. Sjostrom M, Umefjord G, Lindholm L, et al. Cost-Effectiveness of an Internet-Based Treatment Program for Stress Urinary Incontinence. Neurourol. and Urodyn., 2013; 17. [Epub ahead of print]
20. Labrie J, Lagro-Janssen ALM, Fisher K, et al. Predicting who will undergo surgery after physiotherapy for female stress urinary incontinence? Int Urogynecol J 2014; Jul 29. [Epub ahead of print]

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Build-up of the lump sum "Diagnose Treatment Combination" for slingsurgery and conservative management of stress urinary incontinence

	Incontinence Surgery Mean per patient*	Conservative management Mean per patient*
Diagnosis		
Outpatient extra visit	1.24	0.73
Assessment of ECG	0.11	
Cystoscopy	0.03	
Chromocystoscopy	0.02	
Uroflowmetry	0.05	0.03
Urodynamic investigation	0.07	
Operation		
Slingsurgery with colporrhaphy	0.16	
Slingsurgery without colporrhaphy	0.85	
Imaging		
Ultrasound of pelvic organs	0.27	0.28
Clinical chemistry		
Urine screen	0.33	0.10
Urine sediment	0.08	0.03
Urea	0.04	
Glucose	0.18	
Creatinine	0.14	0.03
Sodium	0.10	
Potassium	0.12	
Blood type and screen (ABO)	0.34	
Indirect coombs test	0.01	
C-Reactive Protein	0.04	
Haemoglobin	0.53	0.04
Blood sedimentation	0.02	
Thrombocyte count	0.12	
Blood, qualitative	0.03	
Specific antibodies against human tissue	0.03	
Transaminases	0.04	
Leukocyte count	0.13	
Venepuncture	1.15	0.19
Microbiology and Parasitology		
Microscopic analysis	0.15	0.06
Bacteriological and resistance profile	0.46	
Microbiologic culture 2-3 media	0.15	0.07
Microbiologic culture >3 media	0.04	
Determination micro-organism	0.06	0.03
Pathology		
Histological examination	0.04	
Cytology		0.03

* Number represent a partitioning in the diagnose treatment combination

Supplementary Table 2. Probability of Cost-Acceptability

Threshold (€)	Acceptability of ICER < €80.000
0	0,00%
10.000	0,12%
20.000	2,17%
30.000	10,69%
40.000	25,95%
50.000	43,09%
60.000	56,81%
70.000	66,98%
80.000	74,19%
90.000	79,54%
100.000	83,05%

ICER: Incremental cost effectiveness ratio


7

GENERAL DISCUSSION

GENERAL DISCUSSION

The study described in this thesis was designed to evaluate and optimise initial treatment strategies for women with stress urinary incontinence. In our review of literature we reported that both pelvic floor muscle training (physiotherapy) and midurethral slingsurgery (slingsurgery) significantly improve health related quality of life (HRQoL). We also demonstrated that surgical management improves HRQoL to a greater extent than physiotherapy. However, a direct comparison of both interventions was lacking.

Therefore, we conducted the Physiotherapy OR TVT Randomised Efficacy Trial (PORTRET study) comparing initial physiotherapy and initial slingsurgery for stress urinary incontinence in collaboration with the Dutch Urogynaecologic Consortium. This consortium aims to optimise research through standardisation in the design, execution and reporting of studies. The PORTRET study was one of the first large multicenter trials set up to use their infrastructure.

We demonstrated that women undergoing initial slingsurgery were significantly more likely to show improvement at 12 months than those assigned to receive initial physiotherapy. The crossover rate to slingsurgery after initial physiotherapy was 49% and was higher than anticipated. Slingsurgery resulted in greater improvement than did physiotherapy on all secondary end points. In a subsequent per-protocol analysis, women who underwent additional slingsurgery had significantly more favourable outcomes than women who received physiotherapy only.

To provide an evidence base for counselling on initial treatment strategy we constructed a prediction rule. With this rule it is possible to calculate the chance of slingsurgery within 12 months after starting initial physiotherapy for stress urinary incontinent women.

Before implementation as standard of care, a treatment strategy should be evaluated from both a clinical and an economical perspective. Therefore a cost effectiveness analysis of both initial treatment strategies was performed. This analysis demonstrated that initial slingsurgery is cost-effective. The mean incremental cost-effectiveness ratio (ICER) was € 54.377 with a 74% probability of the ICER remaining below the Dutch threshold of €80.000.

ISSUES IN STUDY DESIGN

The PORTRET study was set up as a pragmatic trial in which treatment strategies, i.e. initial physiotherapy versus initial slingsurgery, rather than separate treatments were compared. This was undertaken by following the intention to treat principle in analysing the data. Performing intention to treat analysis ensures external validity because it follows clinical practice, in which women with stress urinary incontinence undergo additional treatment once the initial treatment is not effective enough.

Patient selection

Bias in the selection of our patient population was a concern. Women with a preference for slingsurgery may have been more likely to participate in the study because outside the trial initial physiotherapy was the standard treatment. This argument also holds up for women

with a preference for initial physiotherapy. When women would have a preference for initial slingsurgery we would expect that they would be less motivated to perform physiotherapy exercises. This could not be demonstrated by our data; the number of physiotherapy sessions was similar in women who did and did not cross over to slingsurgery. We can state that our randomisation was adequate and selection bias was minimised.

Slingsurgery can lead to de novo urgency complaints or aggravate current urgency complaints.[1] Therefore, it is important that the procedure should only be performed in women with predominant or genuine stress urinary continence. Unexpectedly, we observed a higher improvement rate on the score of the overactive bladder domain of the Urogenital Distress Inventory (UDI) in all women who underwent slingsurgery compared to physiotherapy. An explanation for this improvement on overactive bladder complaints probably lies in the lack of specificity for urgency complaints of this UDI-domain.[2] Stress incontinent women with a full bladder, and a consecutive physiological urgency to urinate will lose urine when they are trying to get to a toilet as quickly as possible. This in essence is not urge but stress urinary incontinence.[3] The key to selecting the appropriate women for slingsurgery therefore lies in taking a correct and thorough patient history.

Crossover

When following the intention to treat principle, crossover between treatment arms obscures the interpretation of outcomes. Although we anticipated crossover when designing the trial, we did not expect a 49% crossover rate to slingsurgery after initial physiotherapy within 12 months follow-up.

Questions were raised on the reason for high crossover. An explanation could be that women who underwent unsuccessful physiotherapy entered the trial to gain easy access to initial slingsurgery. Therefore we checked whether there was a difference in the crossover rate between physiotherapy naïve and previously treated women. The percentage of crossover to slingsurgery was similar between women who were treatment naïve (47% crossover) and women who were not (49% crossover) (P=0.86).

Not only the reason for crossover but also the consequences of crossover on outcomes were discussed. Questions were raised on the effectiveness of physiotherapy alone (without surgery). This information is essential in counselling for optimal initial treatment strategies. In order to draw conclusions on physiotherapy alone, we performed an additional per protocol analysis based on treatment regimen. In this analysis, outcomes for women who underwent physiotherapy only, slingsurgery after physiotherapy and initial slingsurgery were presented separately. Our per protocol analysis showed that approximately 30% of women who underwent physiotherapy only considered their symptoms to be improved (much or very much) compared to approximately 90% of women who underwent slingsurgery (initially or additionally) at 12 months follow-up. This supports the conclusion that slingsurgery improves complaints to a greater extent than physiotherapy alone.

We understand that such a post hoc analysis, although initiated by the results of the trial, is not the most correct way to present the results of treatment strategies. Its outcome should be interpreted with caution because our trial was not powered for this analysis. However, basing the analysis on treatment regimen has been defined as the correct approach.[4]

COST-EFFECTIVENESS

When initial treatment strategies are evaluated, it is important to justify a new approach from a cost perspective. Therefore, we reported the cost-effectiveness of initial physiotherapy versus slingsurgery. Where we demonstrated that initial slingsurgery is cost-effective. We found that the crossover rate was the most important driver of the cost-effectiveness of slingsurgery: higher crossover rates will result in higher cost-effectiveness of initial slingsurgery. We also demonstrated that the incremental utilities (score gain on the EuroQol 5D per year) were not influenced by crossover.

For the interpretation of the cost-effectiveness analysis, it is important to consider the technical aspects of measuring outcomes and costs. In the context of outcome assessment, the use of the generic EuroQol 5D questionnaire allows for the calculation of QALYs but it is not disease-specific. Urinary incontinence seems to have a small effect on the HRQoL measured with the EuroQol 5D questionnaire.[5,6] The limited improvement in QALYs, 0.06 for women undergoing initial slingsurgery and 0.07 for initial physiotherapy, are in line with literature.[7,8] Despite the fact that stress urinary incontinence has a strong impact on disease specific HRQoL, woman had high baseline generic HRQoL scores. High baseline scores leave little opportunity for improvement. The EuroQol 5D might be a good instrument to measure QALYs, but unfortunately it lacks responsiveness for incontinence complaints.[5,6,9] QALYs were similar between groups at 12 months follow-up.

In the cost-effectiveness analysis, costs were considered from a societal perspective, including actual treatment cost as well as savings for society. Outcomes from a cost-effectiveness analysis using this perspective are more useful in health policy-making. To calculate health care cost we used the Dutch DBC system (Diagnose-Behandel-Combinatie), which is a complex lump sum system for treatment costs. Presenting the build up of the DBCs and using mean costs derived from all participating hospitals ensured transparency on cost calculations. This enables comparisons with international studies.

The strategy of physiotherapy as initial treatment is not cost-effective if crossover exceeds 40%; in our study population almost 50% of women had crossed over to slingsurgery at 12 months follow-up. The expectancy is that over of time even more women would crossover, making initial slingsurgery more cost-effective. Our cost-analysis further supports our advice to individualise treatment and start initial slingsurgery for selected stress urinary incontinent woman.

CLINICAL IMPLICATIONS

Counselling for treatment strategy

As we have demonstrated initial slingsurgery is cost-effective, but whom should we include in this treatment strategy? To enable adequate counselling, a prediction rule was developed to guide the clinician and stress urinary incontinent woman in the choice of initial treatment strategy. Some women could be better off by starting physiotherapy while others would be better of undergoing initial slingsurgery. The appropriate treatment strategy will differ per woman and in the counselling process all factors that could influence optimal treatment outcomes should

be taken into consideration. The prediction rule provides the risk of undergoing additional slingsurgery within 1 year after starting initial physiotherapy using readily available parameters.

In the prediction rule age <55, higher educational level and severity of incontinence at baseline (measured with the Sandvik index and the Urogenital Distress Inventory) were significantly associated with a higher chance of slingsurgery after initial physiotherapy. Multiple factors could explain why higher educated, younger women were more likely to crossover to slingsurgery. First of all a higher educational level is a proxy for higher socioeconomic status and probably makes it easier to navigate the health care system. Additionally, women with more years of education could have higher levels of self-efficacy, which may facilitate seeking additional treatment when an initial treatment falls short. Another explanation could be that a history of being schooled for a longer period results in an expectancy to overcome obstacles because these women have faced the challenges of overcoming educational requirements such as examinations and standardised tests.[10,11]

Furthermore, higher education is associated with a more active coping strategy.[12,13]whether middle-aged and older adults spontaneously engage in proactive coping to prevent future problems associated with ageing and whether differences in proactive coping were associated with socio-economic status (SES An active coping strategy has been associated with a reduction in sickness absence[14]problem-solving strategies are generally associated with positive results in terms of well-being and overall health outcomes; our hypothesis is that such strategies are positively related to a low frequency of sickness absence and with short lengths (total number of days absent and better problem solving ability which leads to alleviation of stressful situations.[15,16] Therefore women with an active coping strategy are probably more likely to crossover to an alternative treatment option if the initial one fails.

The interaction between health outcomes and educational level is complex and multifactorial. This interaction may include internal person variables (self-efficacy and health literacy) as well as external environmental variables such as insurance information, access to health services and transportation to get medical attention.[10] Highly educated women could have a preference for a quick and effective, effortless solution of their complaints.[11]

To optimise counselling and formulate an advice on treatment strategy we divided women in three risk categories. Women scoring under 5 points (low risk) will have a chance up to 32% of undergoing slingsurgery in the year after starting physiotherapy. For these women a feasible advice would be to start physiotherapy. Women scoring over 10 points (high risk) will have a chance of slingsurgery of 62% or higher and could be counseled more toward initial slingsurgery. However, Most women scored in the intermediate category (5-10 points).

Although most women scored in the intermediate group the prediction rule is still clinically relevant. When counselling for initial treatment strategy in this group, we can apply the more neutral advice on both initial treatment options. This leaves the opportunity to take factors such as personal preference and the expectation of treatment outcome into account. Counselling should include providing information on treatment outcomes and the possible risks of slingsurgery for stress urinary incontinence. By using our prediction rule in individualising initial treatment strategies, counselling will have an evidence based approach.

Counselling on objective and subjective outcomes together with expectancies of treatment outcomes, personal preferences and chance of slingsurgery will enable shared decision making

CONSIDERATIONS CONCERNING VAGINAL IMPLANTS

In light of the recent discussions on vaginal mesh surgery we briefly discuss the considerations on vaginal slingsurgery. The midurethral sling is a relatively small vaginal mesh compared to the meshes used in prolapse surgery. The mesh complications that have been under debate are only seen as a result of prolapse surgery. The U.S. Food and Drug Administration (FDA) found that the safety and effectiveness of slingsurgery for stress urinary incontinence is well established in clinical trials as compared to vaginal mesh surgery for pelvic organ prolapse. They further state that midurethral sling slingsurgery was not the subject of their safety communication in contrast to vaginal mesh surgery. The international Urogynecological Association (IUGA) also supports the use of the midurethral sling in treating stress urinary incontinence and have send out a statement regarding this matter.[17]

RECOMMENDATIONS AND FUTURE RESEARCH

Will there be a paradigm shift?

The difficulty of any trial lies in the implementation of the outcomes. There have been comments on our conclusions and advices. In short, most state that there is no harm in trying physiotherapy first. Then if it fails, slingsurgery should be advised. This point of view is supported in the latest 2014 Cochrane review on pelvic floor muscle training.[18]

We agree that our data do not argue against trying physiotherapy initially. However, we do not agree with trying physiotherapy for *all* stress incontinent women. The principal "physiotherapy does no harm" is often used as an argument to initially try physiotherapy. We have to realise that initial physiotherapy improves HRQoL to a lesser extent and has reported lower cure rates. It carries direct extra costs of the treatment sessions itself, indirect costs related to travel time and costs, time lost from work, prolonged use of sanitary pads, lower quality of life, and compared to initial surgery, it is not cost effective at 12 months follow-up.

The recently updated Dutch guideline on secondary and tertiary care for urinary incontinence has adopted the results from this thesis.[19] It now advised that initial slingsurgery is an initial option for the treatment naïve moderate to severe stress incontinent woman.

Recommendations

In making comparisons between studies we experienced difficulty in performing statistical analysis and drawing conclusions due to heterogeneity in studies, especially due to differences in HRQoL assessment. The International Consultation on Incontinence (ICI) has reviewed all questionnaires that assess HRQoL for women with urinary incontinence extensively.[20] They graded all HRQoL questionnaires from A (highly recommended) to C (questionnaire with potential). In their recommendations they state that a grade A questionnaire should be used in clinical

trails evaluating treatments. Nonetheless, many studies used, non-validated questionnaires or interpreted validated questionnaires incorrectly.[21–23]overactive bladders, associated prolapses, neurovegetative disorders and recurrent SUI or under rehabilitative/medical therapies were all excluded. There were 208 women included. Operating times were longer, and postoperative pain greater for TVT ($p < 0.001$ Only when measuring HRQoL is standardised and comparable measures are used, research can be compared, pooled and meta-analysis undertaken. This problem was also acknowledged by the two Cochrane reviews on physiotherapy and slingsurgery[18,24]

In addition to HRQoL, other patient reported outcomes should be measured. The concept of measuring patient related outcomes is relatively new and the rationale is unclear to many. The evaluation of outcomes, which are meaningful and important to patients and their caregivers, is the essence of this form of research. Patients have a unique perspective that can change and improve the pursuit of clinical questions. Including the input from end-users of care i.e. patients and doctors, will enhance the relevance of research on healthcare decision-making. This increased relevance could lead to improving the likelihood of achieving better health outcomes in the future.[25]

In the Netherlands the "Werkgroep Bekkenbodem" as part of the Dutch Society for Obstetrics and Gynaecology strives to standardise incontinence treatment and evaluate patient reported outcomes. Standardisation of patient reported outcomes for women with urogenital complaints has been pursued with the systematic use of the validated Dutch Incontinence Impact Questionnaire (IIQ) and the Urogentinal Distress Inventory (UDI) as part of the standardised "Werkgroep Bekkenbodem" questionnaire[2,26]severe morbidity and mortality are not associated with this condition. Rather, UI's impact is primarily on the health status and health-related quality of life (HRQOL All clinicians treating urogynecological problems are obliged to inventory patient reported outcomes with this questionnaire. By standardising the evaluation of the full spectrum of health gain, comparisons between hospitals can be made, enabling optimising and auditing of care.

Future research

The follow-up period of the PORTRET study was set at 12 months. As reported recently by Nilsson et al, the objective and subjective cure rates of slingsurgery remain stable over a longer period of follow-up.[27] We intend to perform long-term follow-up of women who participated in the PORTRET study. In further research on our study population we will aim to report on the voluntary long-term adherence to physiotherapy. We are interested in long-term objective and subjective outcomes of both physiotherapy and slingsurgery. Crossover to slingsurgery and crossover to additional physiotherapy after slingsurgery are further interests. By performing long-term follow-up we can adequately inform women with stress urinary incontinence on treatment outcomes. This enables more adequate counselling for treatment strategy.

The prediction rule we presented has been internally validated however external validation needs to be performed in a new population. We plan to validate our prediction rule using data obtained from the "Werkgroep Bekkenbodem" questionnaire. The prediction rule can then be implemented in clinical use after is has been externally validated, ensuring patient centered care.

GENERAL CONCLUSION

With the results presented in this thesis we provide an evidence base for patient centered care in female stress urinary incontinence. The information obtained on both objective and subjective outcomes, cost aspects and predictors of crossover to slingsurgery, can be used to individualise an initial treatment strategy.

REFERENCES

1. Abraham N, Vasavada S. Urgency after a sling: review of the management. Curr Urol Rep. 2014; 15(4):400.
2. Van der Vaart CH, de Leeuw JRJ, Roovers JPWR, et al. Measuring health-related quality of life in women with urogenital dysfunction: the urogenital distress inventory and incontinence impact questionnaire revisited. Neurourol Urodyn. 2003; 22(2):97-104.
3. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/ International Continence Society (ICS) Joint Report on the Terminology for Female Pelvic Floor Dysfunction. Neurourol Urodyn. 2010; 20:4-20.
4. Wang R, Lagakos SW, Ware JH, et al. Statistics in medicine--reporting of subgroup analyses in clinical trials. N Engl J Med. 2007; 357(21):2189-94.
5. Innerkofler PC, Guenther V, Rehder P, et al. Improvement of quality of life, anxiety and depression after surgery in patients with stress urinary incontinence: results of a longitudinal short-term follow-up. Health Qual Life Outcomes. 2008; 6:72.
6. Haywood KL, Garratt AM, Lall R, et al. EuroQol EQ-5D and condition-specific measures of health outcome in women with urinary incontinence: reliability, validity and responsiveness. Qual Life Res. 2008; 17(3):475-83.
7. Imamura M, Abrams P, Bain C, et al. of the effectiveness and cost-effectiveness stress urinary incontinence. Health Technol Assess (Rockv). 2010; 14(40).
8. Richardson ML, Sokol ER. A cost effectiveness analysis of conservative versus surgical management for the initial treatment of stress urinary incontinence. Am J Obstet Gynecol. 2014. [epub ahead of print].
9. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res. 2005; 14(6):1523-1532.
10. Burker EJ, Madan A, Evon D, et al. Educational level, coping, and psychological and physical aspects of quality of life in heart transplant candidates. Clin Transplant. 2009; 23(2):233-40.
11. Kristenson M, Eriksen HR, Sluiter JK, et al. Psychobiological mechanisms of socioeconomic differences in health. Soc Sci Med. 2004; 58(8):1511-22.
12. Ouwehand C, de Ridder DTD, Bensing JM. Who can afford to look to the future? The relationship between socio-economic status and proactive coping. Eur J Public Health. 2009; 19(4):412-7.
13. Feldman P, Steptoe A. Psychosocial and socioeconomic factors associated with glycated hemoglobin in nondiabetic middle-aged men and women. Heal Psychol. 2003; 22:398-405.
14. Van Rhenen W, Schaufeli WB, van Dijk FJH, et al. Coping and sickness absence. Int Arch Occup Environ Health. 2008; 81(4):461-72.
15. Lazarus R. Coping theory and research: past, present, and future. Psychosom Med. 1993; 55:234-247.
16. Huizink A, de Medina P, Mulder E, et al. Coping in normal pregnancy. Ann Behav Med. 2002; 24:132-140.
17. http://www.iuga.org/
18. Dumoulin C, Hay-Smith J. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev. 2014; (5).
19. Nederlandse vereniging voor urologie in samenwerking met de Nederlandse vereniging voor Obstetrie en Gynaecologie. Richtlijn Urine Incontinentie voor de tweede- en derdelijnszorg. 2014 (may).
20. Abrams P, Cardozo L, Khoury S, et al. Incontinence. In: Incontinence, 4th International Consultation on Incontinence. 4th ed. Paris: Health publication Ltd.; 2009; 363-412.
21. Araco F, Gravante G, Sorge R, et al. TVT-O vs TVT: a randomized trial in patients with different degrees of urinary stress incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2008; 19(7):917-26.
22. Porena M, Costantini E, Frea B, et al. Tension-free vaginal tape versus transobturator tape as surgery for stress urinary incontinence: results of a multicentre randomised trial. Eur Urol. 2007; 52(5):1481-90.
23. Rinne K, Laurikainen E, Kivelä A, et al. A randomized trial comparing TVT with TVT-O: 12-month results. Int Urogynecol J Pelvic Floor Dysfunct. 2008; 19(8):1049-54.
24. Ogah J, Cody J, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane database Syst Rev. 2010; (1):CD006375.
25. Frank L, Basch E, Selby JV. The PCORI Perspective on Patient-Centered Outcomes Research. JAMA. 2014;20036.
26. Shumaker SA, Wyman JF, Uebersax JS, et al. Health-related quality of life measures for women with urinary incontinence: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program in Women (CPW) Research Group. Qual Life Res. 1994; 3(5):291-306.

27. Nilsson CG, Palva K, Aarnio R, et al. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2013; 24(8):1265-9.


8

SUMMARY

THESIS SUMMARY

This thesis focussed on the treatment of stress urinary incontinence in women. It comprises the results of the PORTRET study (Physiotherapy OR Tvt Effectiveness Trial). Stress urinary incontinence affects half of all incontinent women and is a bothersome condition. As described in **Chapter 1** the most common treatment options for stress urinary incontinence are pelvic floor muscle training and midurethral slingsurgery and both improve complaints and health related quality of life. Currently, pelvic floor muscle training is advised as initial treatment for all women with stress urinary incontinence. We questioned whether *all* stressincontinent women should initially be treated with pelvic floor muscle training or if slingsurgery could be a good initial treatment option too.

In **Chapter 2** we reviewed literature on the effect of pelvic floor muscle training and midurethral slingsurgery on Health Related quality of life. From a patient's perspective, improving HRQoL is probably equally important as cure of stress urinary incontinence. We conducted a systematic literature search in the PubMed, Embase, and Cochrane databases. Studies were found that reported on health related quality of life after intervention for stress urinary incontinence. Both pelvic floor muscle training and midurethral slingsurgery Improve health related quality of life. However improvement seemed higher after midurethral slingsurgery. Unfortunately the possibility for comparisons between studies was limited because health related quality of life assessment varied widely between studies. We advised to further standardise health related quality of life measures in future reports.

In **Chapter 3** we described the rationale and design of the PORTRET study. As stated in the introduction of the thesis we hypothesised that midurethral sling surgery could be an alternative initial treatment option for selected women with stress urinary incontinence next to pelvic floor muscle training. Women aged 35-80 years old with moderate to severe, predominantly stress, urinary incontinence were randomised to either initial pelvic floor muscle training or initial midurethral slingsurgery. The follow up period was 12 months. The main endpoint of the study was the subjective improvement of urinary incontinence. As secondary outcome objective and subjective cure was assessed. Methods for developing a prediction model are presented and allow for accurate counselling for individualised treatment in future patients with stress incontinence. The economical endpoint was short-term (1-year): incremental cost-effectiveness in costs per additional year free of urinary incontinence and costs per Quality Adjusted Life Years gained.

In **Chapter 4** we presented the main and secondary outcomes of the PORTRET study. Crossover between groups was allowed. The primary outcome was subjective improvement, measured by means of the Patient Global Impression of Improvement at 12 months. We randomly assigned 230 women to the slingsurgery group and 230 women to the physiotherapy group. In the physiotherapy group 49.0% crossed over to the alternative treatment compared to 11.2% of women in the surgery group. We performed an intention-to-treat analysis and subjective improvement was reported by 90.8% of women in the slingsurgery group versus 64.4% of women in the physiotherapy group (95% confidence interval [CI], 18.1 to 34.5). The rates of subjective cure were 85.2% in the slingsurgery group and 53.4% in the physiotherapy group (95% CI, 22.6 to 40.3); rates of objective cure were 76.5% and 58.8%, respectively (95%

CI, 7.9 to 27.3). A post hoc per-protocol analysis showed that women who crossed over to the slingsurgery group had outcomes similar to those initially assigned to slingsurgery and that both these groups had outcomes superior compared to women who did not cross over to slingsurgery. We concluded that for women with stress urinary incontinence, initial midurethral slingsurgery, as compared with initial physiotherapy, results in higher rates of subjective improvement and subjective and objective cure at 12 months follow up. Our findings suggested that women with stress urinary incontinence should be counseled regarding both pelvic floor muscle training and midurethral slingsurgery as initial treatment option.

In **chapter 5** we developed a prediction rule for the chance of slingsurgery after initial physiotherapy in stress urinary incontinent women. The rule was developed with data from 198/230 women who were randomised to physiotherapy in the PORTRET study. Prognostic factors for undergoing slingsurgery after physiotherapy were: age <55 years at baseline (OR 2.87; 95 % CI 1.30–6.32), higher educational level (OR 3.28; 95 % CI 0.80–13.47) and severe incontinence at baseline according to the Sandvik index (OR 1.77; 95 % CI 0.95–3.29) and Urogenital Distress Inventory; incontinence domain score (OR 1.03; per point; 95 % CI 1.01–1.65). The following prediction rule was constructed: *"Chance of slingsurgery = (4*age <55) + (2*Sandvik–severe) + (4*higher educational level) + (0.1*UDI score on incontinence domain) + (–9*(higher educational level*age < 55))"*. We concluded that in women with moderate to severe stress incontinence, individual prediction for slingsurgery after initial physiotherapy is possible, thus enabling shared decision making for the choice between initial conservative or invasive management of stress urinary incontinence. With this rule we are able to counsel on individualised treatment strategy.

Besides identifying the best treatment strategy for the individual woman, health economic evaluations can guide policy makers in optimising treatment approach. In **Chapter 6** we performed an incremental cost-utility analysis of pelvic floor muscle training and slingsurgery. We used prospectively obtained data from the PORTRET study to perform this analysis. Treatment costs were derived from questionnaires at all follow-up moments. Quality of life was measured with the EuroQol 5D questionnaire and the incremental cost per quality adjusted life years i.e. incremental cost-effectiveness ratio (ICER) was calculated. The incremental cost for initial slingsurgery was €1091 (95% CI; 566-1617). The mean ICER for initial slingsurgery was € 54.377 with a 74% probability of the ICER remaining below the Dutch threshold of €80.000 per QALY gained.

We demonstrated that initial midurethral slingsurgery is a cost effective treatment approach compared to initial pelvic floor muscle training for moderate to severe urinary stress incontinent women. From a cost perspective and taking in account objective and subjective outcomes of treatment, both options should be considered as initial treatment approach for SUI.

Chapter 7 discusses the results and conclusions that can be drawn form this thesis in a broader perspective. The information obtained in the research presented in this thesis on both objective and subjective outcomes, predictors of crossover to slingsurgery and cost aspects, can be used to individualise initial treatment strategy for women with stress urinary incontinence.


8

NEDERLANDSE SAMENVATTING

NEDERLANDSE SAMENVATTING

Dit proefschrift richt zich op de behandeling van stressincontinentie bij vrouwen. Het beschrijft de resultaten van de PORTRET studie (Physiotherapy OR Tvt Randomised Efficacy Trial). De helft van alle incontinente vrouwen heeft stress-urine-incontinentie en dit is een beperkende aandoening. Zoals beschreven in **hoofdstuk 1** zijn bekkenfysiotherapie en midurethrale slingchirurgie de meest toegepaste behandelopties. Beide verbeteren incontinentie klachten en de aan gezondheid gerelateerde kwaliteit van leven. Momenteel is het starten met bekkenfysiotherapie de eerste keuze van behandeling voor alle vrouwen met stress-urine-incontinentie. We vroegen ons af of *alle* vrouwen met stressincontinentie in eerste instantie moeten worden behandeld met bekkenfysiotherapie of dat slingchirurgie ook een goede eerste behandeloptie zou kunnen zijn.

In **hoofdstuk 2** geven we een overzicht van de literatuur over het effect van bekkenfysiotherapie en midurethrale slingchirurgie op gezondheid gerelateerde kwaliteit van leven. Vanuit het perspectief van de patiënt, is de verbetering van kwaliteit van leven waarschijnlijk even belangrijk als genezing van stressincontinentie. We zochten systematisch in PubMed, Embase en de Cochrane database naar studies die rapporteerden over gezondheid gerelateerde kwaliteit van leven na behandeling voor stressincontinentie. Zowel bekkenfysiotherapie als midurethrale slingchirurgie verbeteren kwaliteit van leven. Deze verbetering leek echter hoger te zijn na midurethrale slingchirurgie. Helaas was de mogelijkheid voor het vergelijkingen van studies beperkt, omdat de gebruikte instrumenten voor het meten van kwaliteit van leven varieerden tussen de studies. Wij adviseerden in onze conclusie om het meten van kwaliteit van leven verder te standaardiseren in toekomstig onderzoek naar stressincontinentie. Op die manier kan onderzoek effectiever worden verricht en vergeleken.

In **hoofdstuk 3** beschrijven we de rationale en het ontwerp van de PORTRET studie. Zoals wordt vermeld in de inleiding van dit proefschrift was onze hypothese dat midurethrale slingchirurgie voor een geselecteerde groep vrouwen met stressincontinentie een eerste behandeloptie zou kunnen zijn. Vrouwen van 35 tot 80 jaar oud met matige tot ernstige, predominante stressincontinentie werden gerandomiseerd om ofwel initiële bekkenfysiotherapie ofwel initiële midurethrale slingchirurgie te ondergaan. De follow-up periode was 12 maanden. Het primaire eindpunt van de studie was de subjectieve verbetering van stressincontinentie klachten. Als secundaire uitkomst werd gekozen voor objectieve en subjectieve genezing. Verder beschrijven we de methode voor het ontwikkelen van een voorspellingsmodel. Dit model is gericht op adequate counseling om een geïndividualiseerde behandeling van stressincontinentie mogelijk te maken. Het economische eindpunt van de PORTRET studie was de korte termijn (12 maanden) incrementele kosten-effectiviteit.

In **hoofdstuk 4** presenteren we de primaire en secundaire uitkomsten van het PORTRET studie. Het primaire eindpunt was subjectieve verbetering, gemeten met de "Patient Global Impression of Improvement" bij 12 maanden. We randomiseerden 230 vrouwen in de slingchirurgiegroep en 230 vrouwen in de bekkenfysiotherapie groep. In de bekkenfysiotherapiegroep stapte 49,0% over naar de alternatieve behandeling ten opzichte van 11,2% van de vrouwen in de

chirurgiegroep. We voerden een intention-to-treat analyse uit en hierbij werd subjectieve verbetering gemeld door 90,8% van de vrouwen in de slingchirurgie groep versus 64,4% van de vrouwen in de bekkenfysiotherapie groep (95% betrouwbaarheidsinterval [BI], 18,1-34,5). De percentages van subjectieve genezing zijn 85.2% in de slingchirurgiegroep en 53,4% in de bekkenfysiotherapiegroep (95% BI 22,6-40,3). De mate van objectieve genezing zijn respectievelijk 76,5% en 58,8%, (95% CI, 7,9-27,3). Een post hoc per protocol analyse toont aan dat vrouwen die overgegaan waren naar de slingchirurgie vergelijkbare resultaten tonen als vrouwen die aanvankelijk randomiseerden voor slingchirurgie. Tevens rapporteerden deze twee groepen betere uitkomsten dan die van de vrouwen die niet overgingen naar slingchirurgie. Wij concluderen dat vrouwen met stressincontinentie, die initiële slingchirurgie ondergingen, hogere subjectieve verbetering en subjectieve en objectieve genezing hebben bij 12 maanden follow-up dan vrouwen die alleen bekkenfysiotherapie ondergingen. Onze bevindingen suggereren dat vrouwen met stressincontinentie moeten worden voorgelicht over zowel bekkenfysiotherapie en midurethrale slingchirurgie als mogelijke eerste behandeloptie.

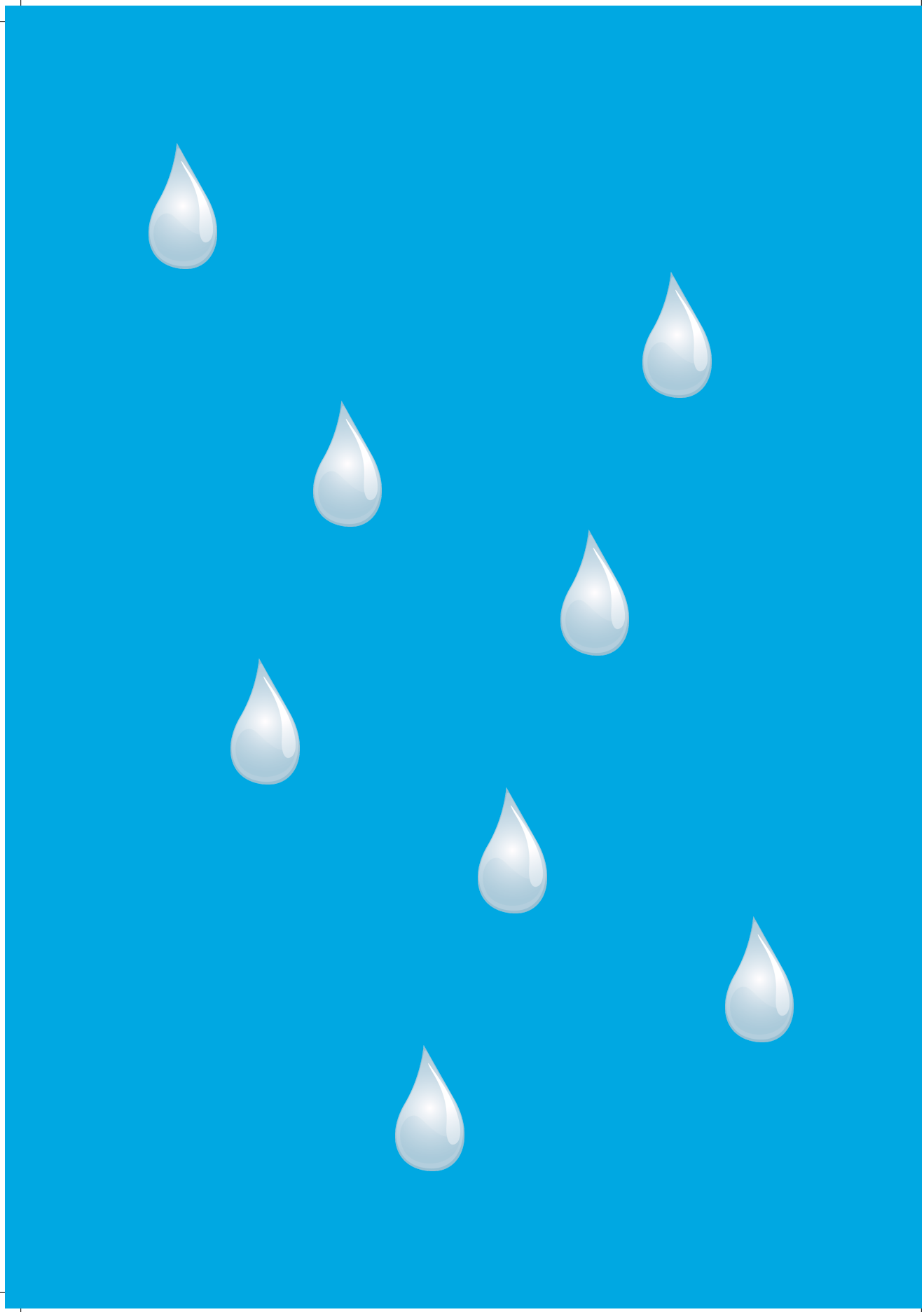
In **hoofdstuk 5** hebben we een voorspellingsregel gemaakt voor de kans op slingchirurgie na initiële bekkenfysiotherapie in stress-incontinente vrouwen. Deze regel is ontwikkeld met gegevens van 198/230 vrouwen die werden gerandomiseerd voor bekkenfysiotherapie in de PORTRET studie. Prognostische factoren voor het ondergaan van slingchirurgie na bekkenfysiotherapie zijn: leeftijd <55 jaar bij aanvang (OR 2,87; 95% CI 1,30-6,32), hoger opleidingsniveau (OR 3,28; 95% BI 0,80-13,47) en ernstige incontinentie bij aanvang volgens de Sandvik index (OR 1,77; 95% CI 0,95-3,29) en Urogenitale Distress Inventory; incontinentie domein score (OR 1,03; per punt; 95% CI 1,01-1,65). De volgende voorspellingsregel werd gemaakt: *"kans op slingchirurgie = (4 * leeftijd <55) + (2 * Sandvik - ernstige) + (4 * hoger opleidingsniveau) + (0,1 * UDI score op incontinentie domein) + (-9 * (hoger opleidingsniveau * leeftijd <55))"*. Wij concluderen dat bij vrouwen met matige tot ernstige stressincontinentie, individuele voorspelling voor slingchirurgie na initiële bekkenfysiotherapie mogelijk is, waardoor gezamenlijke beslissingen voor het kiezen tussen initiële conservatieve of invasieve behandeling van stressincontinentie mogelijk is. Met deze regel kunnen we beter adviseren over een geïndividualiseerde behandelingsstrategie.

Naast het identificeren van de beste strategie voor de behandeling van de individuele vrouw, kunnen gezondheid-economische-evaluaties beleidsmakers begeleiden in de keuze van optimalisatie van behandelaanpak. In **hoofdstuk 6** voerden we een incrementele kosteneffectiviteitsanalyse van bekkenfysiotherapie en slingchirurgie uit. We gebruikten prospectief verkregen gegevens van de PORTRET studie voor deze analyse. De behandelingskosten werden afgeleid van afgenomen vragenlijsten op alle follow-up momenten. Kwaliteit van leven werd gemeten met de EuroQol-5D vragenlijst en de incrementele kosten per quality adjusted life year (QALY) waarmee de incrementele kosteneffectiviteit ratio (ICER) werd berekend. De incrementele kosten voor de initiële slingchirurgie waren € 1.091 (95% CI; 566-1617) per gewonnen QALY. De gemiddelde ICER voor de initiële slingchirurgie was €54,377 per gewonnen QALY met een waarschijnlijkheid van 74% dat deze onder de Nederlandse drempel van € 80,000 per gewonnen QALY blijft.

We hebben aangetoond dat initiële midurethrale slingchirurgie een kosteneffectieve benadering van de behandeling is ten opzichte van de bekkenfysiotherapie voor matige tot

ernstige stress-urine-incontinentie bij vrouwen. Vanuit kostenoverwegingen en rekening houdend met objectieve en subjectieve uitkomsten gepresenteerd in dit proefschrift, moeten beide opties worden beschouwd als mogelijke initiële behandeling van stressincontinentie.

Hoofdstuk 7 bespreekt de resultaten van dit proefschrift en de conclusies die daaruit kunnen worden getrokken in een breder perspectief. De resultaten van dit proefschrift kunnen worden gebruikt om een initiële behandelstrategie voor vrouwen met stress-urine-incontinentie te individualiseren.



APPENDICES

LIST OF CO-AUTHORS

A.H. Adriaanse
Department of Obstetrics and Gynaecology
Medical Centre Alkmaar, Alkmaar

L.C.M. Berghmans
Department of Urology
University Medical Centre Maastricht, Maastricht

E.E. Blokhuis
Department of Obstetrics and Gynaecology
Zuwe Hofpoort Hospital, Woerden

J.F.G.M. Brouns
Department of Obstetrics and Gynaecology
Zaans Medical Centre, Zaandam

E. Buskens
Department of Epidemiology
University Medical Centre Groningen, Groningen

K. Fischer
Julius Centre for Health Sciences and Primary Care
University Medical Centre Utrecht, Utrecht

Y. van der Graaf
Julius Centre for Health Sciences and Primary Care
University Medical Centre Utrecht, Utrecht

G.C.M. Graziosi
Department of Obstetrics and Gynaecology
Sint Antonius Hospital, Nieuwegein

A.G. Groenendijk
Department of Obstetrics and Gynaecology
Onze lieve vrouwen gasthuis, Amsterdam

R.A. Hakvoort
Department of Obstetrics and Gynaecology
Spaarne Hospital, Hoofddorp

M.H. Kerkhof
Department of Obstetrics and Gynaecology
Isala Hospital, Zwolle

A.L.M. Lagro-Janssen
Department of Primary and Community Care
Radboud University Medical Centre, Nijmegen

A.L. Milani
Department of Obstetrics and Gynaecology
Reinier de Graaf Hospital, Delft

B.W.J. Mol
Department of Obstetrics and Gynaecology
Academic Medical Centre Amsterdam, Amsterdam

J.M. v/d Ploeg
Department of Obstetrics and Gynaecology
Martini Hospital, Groningen

J.P.W.R. Roovers
Department of Gynaecology
Academic Medical Centre Amsterdam, Amsterdam

R.P. Schellart
Department of Obstetrics and Gynaecology
Kennemer Hospital, Haarlem

P.C. Scholten
Department of Obstetrics and Gynaecology
Diakonessenhuis Hospital, Utrecht

A. Schram
Department of Obstetrics and Gynaecology
University Medical Centre Groningen, Groningen

D.J.C. Smalbraak
Department of Obstetrics and Gynaecology
Amphia Hospital, Breda

E.S.M. Tiersma
Department of Obstetrics and Gynaecology
VU University Medical Centre, Amsterdam

C.H. van der Vaart
Department of Gynaecology
University Medical Centre Utrecht, Utrecht

A. Vollebregt
Department of Obstetrics and Gynaecology
Spaarne Hospital, Hoofddorp

I. v/d Wijk,
Department of Obstetrics and Gynaecology
Groene Hart Hospital, Gouda

LIST OF ABBREVIATIONS

BFLUTS	Bristol Female Lower Urinary Tract Symptom
CI	Confidence Interval
DBC	Diagnose Behandel Combinatie (Diagnosis Treatment Combination)
EQ-5D	EuroQol 5D
GP	General Practitioner
HRQoL	Health Related Quality of Life
ICER	Incremental cost-effectiveness ratio
ICI	International Continence Society
ICIQ-UI SF	International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form
ICS	International Continence Society
IIQ	Incontinence Impact Questionnaire
I-Qol	Urinary Incontinence Quality of Life Scale
ISLY	Incontinence Severity weighted Life Year
KHQ	Kings Health Questionnaire
NICE	National Institute for Health and Clinical Excellence
OR	Odds Ratio
PGI-I/S	Patient Global Impression of Improvement/Severity
POP-Q	Pelvic Organ Prolapse Quantification
PORTRET	Physiotherapy OR Tvt Randomised Efficacy Trial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
SUI	Stress Urinary Incontinence
SD	Standard Deviation
SPSS	Statistical package for the social sciences
TVT(O)	Tension free Vaginal Tape (Obturator)
UDI	Urinary Distress Incontinence
UMCU	University Medical Centre Utrecht

QUESTIONNAIRES

Baseline gegevens

1. Wat is uw leeftijd? .... jaar

2. Wat is uw burgelijke staat? (Slechts één antwoord mogelijk.)
   1. gehuwd
   2. samenwonend
   3. gescheiden
   4. weduwe
   5. nooit gehuwd geweest

3. Welke opleiding(en) heeft u voltooid? (hoogste opleiding omcirkelen)
   1. basisonderwijs/lagere school (of een deel daarvan)
   2. lager beroepsonderwijs (lts, lhno, leao, huishoudschool etc.)
   3. mavo, (m)ulo etc.
   4 middelbaar beroepsonderwijs (mts, mhno, meao, opleiding tot verpleegkundige etc.)
   5. vwo, havo, gymnasium, mms etc.
   6. hoger beroepsonderwijs (hts, hhno, heao, sociale academie etc.)
   7. wetenschappelijk onderwijs (doctoraal examen)

4. Wat is uw huidige beroep of zijn uw werkzaamheden?
   .....

5. a. Bent u wel eens bevallen? Ja / Nee
   b. Hoeveel kinderen heeft u? . .... (aantal)
   c. Heeft u een keizersnede gehad? Ja (.....keer) / Nee
   d. Heeft u een tang verlossing gehad? Ja (.....keer) / Nee
   e. Heeft u een vacuümcup verlossing gehad? Ja (.....keer) / Nee
   f. Bent u tijdens de bevalling "ingeknipt" Ja (.....keer) / Nee
   g. Bent u tijdens de bevalling "ingescheurd" Ja (.....keer) / Nee
   h. Wanneer was uw laatste bevalling? ..... (dag/maand/jaar)

Dit deel van de vragenlijst bevat een aantal algemene vragen. Omcirkel het bij u passende antwoord of vul de vraag in .

6a. Gebruikt u medicijnen?

Ja / Nee

↓

Naam medicijn:

b. Bent u in de overgang (U heeft meer dan 12 maanden geen vaginaal bloedverlies meer gehad)?

Ja / Nee

↓

Wanneer was uw laatste menstruatie? [__][__] / [__][__][__][__] (maand/jaar)

c. Gebruikt u medicijnen tegen overgangsklachten?

Ja / Nee

↓

Naam medicijn:

d. Rookt u?

Ja / Nee

↓

Wat rookt u ? .....

Hoeveel per dag rookt u? .....

Hoelang rookt u al ? .....

e. Heeft u in het verleden gerookt, maar bent u nu gestopt?

Ja / Nee

↓

Hoeveel jaren heeft u gerookt ? .....

f. Drinkt u alcohol ?

Ja / Nee

↓

Hoeveel glazen alcohol per week ? .....

g. Van wie heeft u bekkenbodemoefeningen gekregen?

1. geen
2. huisarts
3. fysiotherapeut
4. via erkend bekkenbodemfysiotherapeut

h. In welk land bent u geboren? .....
   i. En uw moeder? .....
   j. Wat is uw lengte? .....cm
   k. Wat is uw gewicht: ..... kg

Patient Global Impression of Improvement (PGI-I)

U hebt een behandeling ondergaan voor uw plas en/of verzakkingsklachten. Kies uit onderstaand rijtje het antwoord dat het beste weergeeft hoe uw situatie nu is ten opzichte van de situatie zoals die was vóór dat u werd behandeld.

---

1. heel veel beter
2. veel beter
3. beetje beter
4. geen verandering
5. beetje slechter
6. veel slechter
7. heel veel slechter

Patient Global Impression of Severity

U heeft plas en/of verzakkingsklachten. Kies uit onderstaand rijtje het antwoord dat het beste weergeeft hoe de ernst van uw situatie nu is.

---

1. niet ernstig
2. mild
3. matig
4. ernstig

Sandvik Index

1. *Hoe vaak heeft u last van urine verlies?*
    1. minder dan 1 keer per maand
    2. 1 tot meerdere keren per maand
    3. 1 tot meerdere keren per week
    4. dagelijks
2. *Als u urine verlies heeft verlies u dan voornamelijk druppels of meer dan druppels?*
    1. Druppels
    2. Meer dan druppels

Urogenital Distress Inventory (UDI)

1. a. Vindt u dat u vaak moet plassen?
   1 Ja 2 Nee (ga naar 2.)
   ↓
   b. Zo ja, hoeveel last heeft u hier van?
   1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg

2. a. Als u moet plassen voelt u dan altijd een sterke aandrang?
   1 Ja 2 Nee (ga naar 3.)
   ↓
   b. Zo ja, hoeveel last heeft u hier van?
   1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg

3. a. Heeft u ongewenst urineverlies als u aandrang voelt om te plassen?
   1 Ja 2 Nee (ga naar 4.)
   ↓
   b. Zo ja, hoeveel last heeft u hier van?
   1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg
   c. Zo ja, hoe vaak verliest u ongewild urine?
   1. dagelijks
   2. paar keer per week
   3. 1 keer per week
   4. 1 keer per maand
   5. 1 keer per jaar

4. a. Heeft u ongewenst urineverlies bij lichamelijke inspanning, hoesten of niezen?
   1 Ja 2 Nee (ga naar 5.)
   ↓
   b. Zo ja, hoeveel last heeft u hier van?
   1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg
   c. Zo ja, hoe vaak verliest u ongewild urine?
   1. dagelijks
   2. paar keer per week
   3. 1 keer per week
   4. 1 keer per maand
   5. 1 keer per jaar

5. a. Heeft u wel eens ongewenst urineverlies zonder dat u aandrang voelt of zonder dat u zich lichamelijk inspant?
   1 Ja 2 Nee (ga naar 6.)
   ↓
   b. Zo ja, hoeveel last heeft u hier van?
   1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg

6. a. Verliest u ongewenst wel eens kleine hoeveelheden urine (druppels)?
   1 Ja 2 Nee (ga naar 7.)
   ↓
   b. Zo ja, hoeveel last heeft u hier van?
   1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg

7. a. Verliest u ongewenst wel eens grote hoeveelheden urine?
   1 Ja 2 Nee (ga naar 8.)
   ↓
   b. Zo ja, hoeveel last heeft u hier van?
   1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg

8. a. Moet u ‘s nachts meerdere keren plassen?
   1 Ja 2 Nee (ga naar 9.)
   ↓
   b. Zo ja, hoeveel last heeft u hier van?
   1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg

9. a. Plast u wel eens in uw bed?
   1 Ja 2 Nee (ga naar 10.)
   ↓
   b. Zo ja, hoeveel last heeft u hier van?
   1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg

10. a. Heeft u moeite uw blaas leeg te plassen?
   1 Ja 2 Nee (ga naar 11.)
   ↓
   b. Zo ja, hoeveel last heeft u hier van?
   1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg

11. a. Heeft u wel een het gevoel dat de blaas na het plassen niet helemaal leeg is ?
   1 Ja 2 Nee (ga naar 12.)
   ↓
   b. Zo ja, hoeveel last heeft u hier van?
   1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg

12. a. Heeft u wel eens een drukkend gevoel onder in de buik?
   1 Ja 2 Nee (ga naar 13.)
   ↓
   b. Zo ja, hoeveel last heeft u hier van?
   1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg

13. a. Heeft u wel eens pijn tijdens het plassen?
    1 Ja 2 Nee (ga naar 14.)
    ↓
    b. Zo ja, hoeveel last heeft u hier van?
    1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg

14. a. Heeft u wel eens pijn onder in de buik of in de schaamstreek?
    1 Ja 2 Nee (ga naar 15.)
    ↓
    b. Zo ja, hoeveel last heeft u hier van?
    1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg

15. a. Heeft u wel eens een zwaar of drukkend gevoel in het bekken gebied?
    1 Ja 2 Nee (ga naar 16.)
    ↓
    b. Zo ja, hoeveel last heeft u hier van?
    1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg

16. a. Heeft u wel eens het gevoel dat er iets uit de vagina stulpt?
    1 Ja 2 Nee (ga naar 17.)
    ↓
    b. Zo ja, hoeveel last heeft u hier van?
    1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg

17. a. Heeft u wel eens gezien dat er iets uit de vagina stulpt?
    1 Ja 2 Nee (ga naar 18.)
    ↓
    b. Zo ja, hoeveel last heeft u hier van?
    1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg

18. a. Heeft u wel eens een ongemakkelijk gevoel in het bekken gebied als u staat of als u zich lichamelijk inspant?
    1 Ja 2 Nee (ga naar 19.)
    ↓
    b. Zo ja, hoeveel last heeft u hier van?
    1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg

19. a. Moet u wel eens tegen de vaginawand drukken om uw ontlasting kwijt te raken?
    1 Ja 2 Nee
    ↓
    b. Zo ja, hoeveel last heeft u hier van?
    1 Helemaal niet 2 Een beetje 3 Nogal 4 Heel erg

Incontinence Impact Questionnaire (IIQ)

Hoeveel invloed heeft ongewenst urineverlies en/of verzakking en/of problemen met de ontlasting gehad op:

---

1. Uw vermogen om huishoudelijk werk te doen (koken, schoonmaken, wassen)
   1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg
2. Uw vermogen om klein onderhoud of reparaties te verrichten in en om het huis
   1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg
3. Boodschappen doen en winkelen
   1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg
4. Hobby's en vrijetijdsbesteding
   1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg
5. Actieve ontspanning zoals wandelen, zwemmen of andere activiteiten
   1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg
6. Activiteiten zoals naar de film, theater of concert gaan
   1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg
7. Reizen met auto of openbaar vervoer over een afstand van minder dan 20 minuten
   1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg
8. Reizen met auto of openbaar vervoer over een afstand van meer dan 20 minuten
   1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg
9. Ergens naar toe gaan als u niet helemaal zeker weet of er daar toiletten zijn
   1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg
10. Op vakantie gaan
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg
11. Naar de kerk, moskee of synagoge gaan
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg
12. Vrijwilligerswerk
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg
13. Betaald werk buitenshuis
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg
14. Bezoek krijgen van vrienden en kennissen
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg

15. Deelnemen aan sociale activiteiten buitenshuis
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg

16. Relaties met vrienden en kennissen
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg

17. Relaties met familie en gezin behalve uw partner / echtgenoot
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg

18. Vermogen om een seksuele relatie te hebben
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg

19. Keuze van kleding
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg

20. Geestelijke / emotionele gezondheid
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg

21. Lichamelijke gezondheid
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg

22. Slapen
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg

23. Wordt u in uw activiteiten beperkt door angst dat anderen u ruiken?
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg

24. Beperkt de angst om in verlegenheid gebracht te worden u in uw activiteiten?
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg

Heeft u als gevolg van uw probleem de volgende gevoelens ?

25 Nervositeit of ongerustheid
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg

26 Angst
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg

27 Frustratie
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg

28 Boosheid
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg

29 Depressie
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg

30 Zich gegeneerd voelen
    1. Helemaal niet 2. Een beetje 3. Nogal 4. Heel erg

EuroQol 5-D

1. Mobiliteit (Slechts één antwoord aankruisen)
   - ❑ Ik heb geen problemen met lopen
   - ❑ Ik heb enige problemen met lopen
   - ❑ Ik ben bedlegerig

2. Zelfzorg (Slechts één antwoord aankruisen)
   - ❑ Ik heb geen problemen om mijzelf te wassen of aan te kleden
   - ❑ Ik heb enige problemen om mijzelf te wassen of aan te kleden
   - ❑ Ik ben niet in staat mijzelf te wassen of aan te kleden

3. Dagelijkse activiteiten bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten (Slechts één antwoord aankruisen)
   - ❑ Ik heb geen problemen met mijn dagelijkse activiteiten
   - ❑ Ik heb enige problemen met mijn dagelijkse activiteiten
   - ❑ Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren

4. Pijn/klachten (Slechts één antwoord aankruisen)
   - ❑ Ik heb geen pijn of andere klachten
   - ❑ Ik heb matige pijn of andere klachten
   - ❑ Ik heb zeer ernstige pijn of andere klachten

5. Stemming (Slechts één antwoord aankruisen)
   - ❑ Ik ben niet angstig of somber
   - ❑ Ik ben matig angstig of somber
   - ❑ Ik ben erg angstig of somber

Kostenmeting

De volgende vragen gaan over bezoek aan ziekenhuis/arts/fysiotherapeut in verband met de incontinentieklachten en gedurende de afgelopen 2 maanden.

In de afgelopen 2 maanden

1. bezocht ik het **ziekenhuis**.....eer
   afstand van huis naar ziekenhuis.....km
   gemiddelde *totale duur* van reis en bezoek.....uur
2. aantal dagen **opname in ziekenhuis**.....dagen
3. bezocht ik de **huisarts** .....keer
   afstand van huis naar huisarts.....km
   gemiddelde *totale duur* van reis en bezoek.....uur
4. bezocht ik de **fysiotherapeut** .....keer
   afstand van huis naar fysiotherapeut.....km
   gemiddelde *totale duur* van reis en bezoek.....uur

INCONTINENTIEMATERIAAL

6. Hoe veel incontinentieverbandjes gebruikt u *gemiddeld* per 24 uur, dus vanaf het moment van opstaan tot de volgende ochtend. U kunt meerdere typen verband gebruiken, en kunt dus meerdere mogelijkheden aankruisen.
   - ❑ inlegkruisjes.....stuks
   - ❑ maandverband.....stuks,
   - ❑ incontinentie verband type: (small, medium, enz).....
     Aantal:.....stuks
   - ❑ incontinentie broekjes type: (small, medium, enz).....
     Aantal:.....stuks

&

Vragenlijst over ziekte en werk.

In deze vragenlijst wordt gevraagd naar gevolgen van incontinentieproblemen voor betaald werk. Er zijn geen "goede" of "foute" antwoorden. Het gaat ons alleen om uw persoonlijke mening. Denk voor uw situatie steeds aan de afgelopen twee maanden.

---

1. Heeft u betaald werk?
   Zo nee, ga verder met vraag 3
   Zo ja, Aantal uur per week.....
   Aantal dagen per week.....
   Beroep.....

2. In de afgelopen 2 maanden. Hoeveel dagen heeft u zich ziek gemeld wegens incontinentieproblemen? 0-62.....dagen

3. U heeft geen betaald werk, welke situatie is het meest op u van toepassing? (kruis aan)
   - ❑ ik heb een dagtaak aan zorg voor huishouden en eventueel kinderen
   - ❑ ik ben gepensioneerd of met de VUT
   - ❑ ik ben student/ volg een opleiding
   - ❑ ik kan geen betaald werk doen wegens gezondheidsproblemen
   - ❑ ik doe geen betaald werk om andere redenen (bv onvrijwillige
   - ❑ werkeloosheid, vrijwilligerswerk, etc)

Mensen met incontinentieproblemen moeten daarvoor soms verzuimen van hun werk. Het kan echter ook voorkomen dat ze wèl op hun werk zijn, maar toch hun werk minder goed kunnen doen vanwege incontinentieproblemen. Daarover gaan de vragen 4 t/m 7.

---

4 Hoeveel **dagen** in de afgelopen **twee weken** bent u wél naar uw werk geweest, terwijl u last had van incontinentieproblemen? LET OP: dagen dat u zich ziek heeft gemeld niet meerekenen.
..... Dagen

5 Hoeveel **uur**, in de afgelopen twee weken is uw betaald werk beïnvloed door incontinentie-problemen? LET OP: dagen dat u zich ziek heeft gemeld niet meerekenen.
..... Uur

6 Hoe vaak bent u in de afgelopen twee weken **eerder** weggegaan van uw werk i.v.m. incontinentieproblemen?
..... gemiddeld .....uur per keer

7 Hoe vaak bent u in de afgelopen twee weken **later** gekomen op uw werk i.v.m. incontinentieproblemen?
.....keer gemiddeld .....uur per keer

DANKWOORD

Het zit erop, het is af. Eindelijk!

Wat lang, lang geleden begon als een wetenschappelijke stage heeft er toe geleid dat dit boek tot stand is gekomen. Veel mensen ben ik dank verschuldigd voor hun inzet, steun, enthousiasme en hulp. Aan enkele van hen wil ik graag nog een woord van dank richten.

Allereerst gaat mijn dank uit naar alle vrouwen die hebben geparticipeerd in de PORTRET studie. Anderhalf jaar lang vragenlijsten invullen en daarnaast ook nog eens incontinentie verbandjes sparen is niet niks. Zonder uw input zou onze studie niet mogelijk zijn geweest. U heeft een enorme bijdrage geleverd om in de toekomst vrouwen met urineverlies adequater te kunnen helpen.

Prof. Dr. C.H. van der Vaart, beste Huub, ik zie mezelf nog zitten de eerste keer bij Alant Vrouw in Zeist. Inmiddels zijn er veel zaken veranderd. Zeist werd ingeruild voor Bilthoven, Alant werd Bergman Vrouwenzorg en jij werd professor. Al die tijd bleef je trekken aan de PORTRET studie naast al je andere drukke bezigheden. Je bent een man van verschillende gezichten elk passend bij hun eigen situatie. Je wilt het onderste uit de kan hebben en daarom kom je tot grote resultaten. Zonder jouw inspiratie, inzet en onuitputtelijke en noodzakelijke aansporingen was dit proefschrift, maar zeker het kroonstuk in de New England er nooit gekomen. Het kan niet anders dan dat ik je zo nu en dan tot wanhoop heb gedreven maar gelukkig kunnen we nog steeds goed door één deur. Dank voor alles, je bent een voorbeeld!

Prof. Dr. A.L.M. Lagro-Janssen, beste Toine, je was reeds betrokken bij de opzet van de PORTRET studie en in een later stadium werd je mijn tweede promotor. Dank voor alle snelle antwoorden en aanvullingen bij het schrijven van de artikelen en de introductie en discussie van dit proefschrift. De blik vanuit het perspectief van de huisarts is van grote waarde geweest.

Dr. K Fischer, beste Kathelijn, wat ben ik dankbaar dat jij bij de PORTRET studie betrokken raakte. Een no-bullshit no-nonsense houding. Een epidemioloog (en wereldberoemd kinder-haematoloog) met een klinische blik. Jij zal me af en toe vast wel achter het behang hebben willen plakken. De eeuwige 5 minuutjes van mij, bij jou thuis, op de van Kreveld of via de whatsapp zorgden ervoor dat ik weer goede zin had en zag hoe het verder moest. Het is heerlijk om samen te werken met iemand bij wie je aan een half woord genoeg hebt. Je bent geweldig, iets wat niet is uit te drukken in een kosteneffectiviteitsplane!

Dr. L.C.M. Berghmans, beste Bary, je bent vanaf het begin betrokken geweest bij de opzet van de PORTRET studie en later ook als co-promotor. Dat jij je als fysiotherapeut aan de PORTRET studie lieerde getuigt van inzicht en het beste met de patiënt voorhebben. Dank voor je snelle antwoorden en kritische noten bij het schrijven van de manuscripten.

De beoordelingscommissie bestaande uit: mw. Prof. dr. J.G. van der Bom, Prof. dr. J.L.H.R. Bosch, Prof. dr. A.A.B. Lycklama à Nijeholt, Prof. dr. M.E. Vierhout en Prof. dr. N.J. de Wit, wil ik hartelijk danken voor het kritisch doornemen van mijn proefschrift.

Alle participerende gynaecologen van de PORTRET studie en mede-auteurs ben ik dank verschuldigd voor hun tomeloze inzet, met name tijdens de inclusieperiode van de PORTRET

studie en het doornemen van de manuscripten. Fred Milani wil ik bedanken voor het grote aantal inclusies in zijn ziekenhuis. Jouw nooit aflatende complimenten en positivisme hebben me altijd veel goed gedaan tijdens de werkgroep bekkenbodem of op congres. Dank Fred! Jan Paul Roovers en Ben Willem Mol wil ik danken voor hun grote inzet voor het (Urogynaecologisch) Consortium.

Lieve Ingrid, Tessa en Ellis. Als onderzoeker had ik al snel door dat wanneer er iets geregeld moest worden ik bij jullie moest zijn. Dank voor jullie hulp op alle gebieden. Tessa zonder jou was ik nooit in opleiding gekomen ;-), je hebt geloof ik nog een chocoladetaart tegoed. Ellis toen jij de secretaresse werd van Huub heb ik nog vaker je hulp moeten inroepen om een plekje te krijgen in zijn drukke agenda. Jullie drie zijn goud waard! Ik ga onze roddelmomentjes wel missen nu ik niet meer in de academie werk.

Drs. K.J. Schweitzer, lieve Karlijn, we kennen elkaar vanaf het moment dat je bij Alant Vrouw begon en ik nog co-assistent was. Inmiddels heb ik veel van je geleerd op meer vlakken dan alleen maar de (uro)gynaecologie. Op de een of andere manier doorzie jij mij (en de rest) perfect, sla je de spijker op zijn kop en doen jouw corrigerende tikjes nooit zeer. Dank dat je mijn mentor wilde zijn tijdens mijn academische stages. Ik hoop nog veel met je samen te werken in de toekomst, ik heb enorme bewondering voor je.

Alle gynaecologen van het Meander Medisch Centrum, jullie hebben me een geweldig eerste jaar van de opleiding bezorgd. Met beperkte ervaring kwam ik in het oude gezellige Elisabeth ziekenhuis, waar jullie mij de beginselen van de gynaecologie en obstetrie hebben bijgebracht. Mijn verhalendoos is enorm gevuld en niet met louter gynaecologische vertellingen! Jitze, een betere opleider had ik me in mijn eerste opleidingsjaar niet kunnen wensen.

Beste medewerkers en onderzoekers van het consortium, het consortium is te groot geworden om iedereen nog bij naam te noemen. Ik vind het geweldig dat ik onderdeel ben van deze unieke groep in Nederland. Ik hoop dat de toekomst nog vele mooie publicaties en proefschriften zal brengen.

Alle mede-onderzoekers van het UMC Utrecht, een beetje een vreemde eend in de bijt was ik wel met mijn plasonderzoek. Dank voor alle gezellige momenten en de maandagmiddag lunches. Op naar groot succes voor jullie allemaal.

Alle mede-AIOS gynaecologie en obstetrie van cluster Utrecht, we zitten in een geweldige en hechte groep die elkaar steunen bij succes en tegenslag. Ik ben er trots op dat ik onderdeel uitmaak van Clustertje 1.

Lieve Utrecht-geneeskunde-meisjes en alle (wisselende) aanhang van de afgelopen jaren. We maken gelukkig nog steeds tijd voor elkaar en de wijn vloeit altijd rijkelijk. Heerlijk om zo'n basisgroep te hebben om op terug te kunnen vallen en waar iedereen zichzelf kan zijn. Dat jullie mijn botte opmerkingen nog niet zat zijn is me een raadsel maar het wordt gewaardeerd!

Lieve Francis, we zien elkaar te weinig maar ik denk nog vaak aan je. Als jij niet in mijn leven was gekomen had het er vast heel anders uitgezien. Ons strootje brandt al jaren niet meer maar je hebt een speciaal plekje in mijn hart.

Lieve vrienden en vriendinnen, jullie zijn er te veel om bij naam te noemen. Ik ben zo blij dat ik af en toe, nou ja af en toe... stoom kan afblazen met een klein drankje in de hand. Of dat nou bij een van jullie thuis is of in de kroeg, het is geweldig dat ik bij jullie, zonder mijn gevoel voor enige nuance of subtiliteit, mezelf kan zijn. Uit angst iemand te vergeten een groot generaal dank aan jullie allemaal.

Lieve Marjolein, Let, waar een werkgroep en enige gelijkenis met je broertje al niet goed voor kan zijn. Inmiddels hebben we over de jaren veel avonturen beleefd. We staan hetzelfde in het leven en hebben nog steeds de grootste lol. Jouw vriendschap is van onschatbare waarde en ik ben blij dat je naast me staat op deze dag, zoals ik dat vorige jaar bij jou mocht doen. Die 7 jaar hebben we al lang en breed gehaald dus het zal wel voor de rest van ons leven duren. Ibiza here we come.

Lieve Anna, als er iemand is die ik 's nachts uit haar bed mag bellen ben jij het wel. Samen met Marjolein hebben we ons een weg geploeterd door geneeskunde, horeca-werk en menig feestje. Het is heerlijk om zo'n gekke en lieve vriendin te hebben die het liefste de hele moederkloek bij elkaar wil houden. Ik heb enorme bewondering voor je keuzes in de afgelopen jaren en je enorme doorzettingsvermogen. Ik hoop dat je nu echt je plek hebt gevonden. Fijn dat je naast me staat op deze belangrijke dag.

Lieve Peter, Marriet, Cathalijn en Oscar, na 9 jaar zijn jullie de grootste schrik inmiddels wel bekomen. Fijn om zo'n gezellige schoonfamilie te hebben. Dank voor jullie interesse in mijn onderzoek, opleiding en leven samen met Matthijs.

Lieve Oma La, geweldig dat u er bij bent vandaag. Op naar de 100

Lieve grote zus Lindsey en Jos, onze levens zouden niet verschillender kunnen zijn en dat maakt het juist leuk. Nu er weer een beetje meer ruimte is beloof ik dat ik vaker langs kom. Bedankt voor de nuchtere kijk op het leven, de gezelligheid en de overvloed aan eten, taarten en koekjes.

Lieve Abby, je bent de trots van de familie en het grootste cadeau van de afgelopen jaren. Je bent het leukste nichtje van de hele wereld.

Lieve Pap en Mam, bedankt voor jullie liefde. Nooit heb ik me hoeven verdedigen in mijn keuzes en altijd hebben jullie me mijn eigen gang laten gaan. Het is heerlijk om te voelen dat jullie me overal in steunen en trots op me zijn. Dankzij jullie ben ik wie ik ben en heb ik al jong geleerd dat het Rotterdamse: "niet lullen maar poetsen" echt werkt. Ik hou van jullie.

Lieve Matthijs, dat wij elkaar nog op de ouderwetse manier hebben ontmoet en nog steeds samen zijn is volgens mij een unicum. We zijn elkaars tegenpolen op veel gebieden en dat is heerlijk. Ik ben zo blij dat je geen dokter bent maar er toch zoveel van begrijpt. De vrijheid die we elkaar geven heeft ertoe geleid dat het nu echt af is en we verder kunnen. Na 63 (9*7) gay-years samen is er eindelijk tijd voor de volgende stappen. Dat trouwen zal nog minimaal een tiental jaren moeten wachten want ik moet opnieuw beginnen met sparen na deze mijlpaal ;-).

Ik hou zielsveel van je!

CURRICULUM VITAE

Julien Labrie werd geboren op 28 januari 1983 in het Havenziekenhuis te Rotterdam. Hij groeide samen met zijn zus op in een echt kappersgezin te Nieuwerkerk aan den IJssel. Na het cum laude behalen van zijn VWO diploma aan het Emmauscollege te Rotterdam startte hij in 2001 met de opleiding Geneeskunde aan de Universiteit van Utrecht. Gedurende zijn co-schap gynaecologie in het Mesos MC te Utrecht werd tegen elke verwachting in zijn interesse voor dit vakgebied gewekt. Vervolgens werd zijn enthousiasme voor de gynaecologie bevestigd na een aanvullend co-schap in het Zuwe Hofpoort Ziekenhuis te Woerden. Omdat de keuze voor zijn specialisatie was gemaakt, wendde hij zich in 2007 tot (toen nog) dr. Van der Vaart in het Universitair Medisch Centrum Utrecht voor een wetenschappelijke stage en oudste co-schap urogynaecologie bij Alant Vrouw te Zeist en later te Bilthoven. Deze stage resulteerde in de aanstelling als arts-onderzoeker van de "Physiotherapy OR Tvt Randomised Efficacy Trial". Hij ontving in 2012 de prijs voor beste podium presentatie door een fellow op de bijeenkomst van de "International Urogynecological Association" te Brisbane Australië. Naast het afronden van zijn proefschrift is hij sinds 1 oktober 2011 gestart met de opleiding tot gynaecoloog. Het eerste jaar werd gevolgd in het Meander MC te Amersfoort (opleider dr. M.J. Duk). Daarna werd de opleiding voortgezet in het Wilhelmina Kinderziekenhuis (WKZ) en het Academisch Ziekenhuis Utrecht (AZU) beiden onderdeel van het Universitair Medisch Centrum Utrecht (opleider Prof. Dr. A. Franx). Per 1 januari 2015 is hij gestart met het laatste deel van zijn opleiding in het Twee Steden Ziekenhuis te Tilburg (opleider dr. H.J.H.M. van Dessel). Sinds 2006 is hij erg gelukkig samen met Matthijs Verweij en na het afronden van zijn promotie zullen zij dan eindelijk gaan samenwonen.

Your life is a sham till you can shout out:
I am what I am!

From: La cage aux folles, Jerry Herman; 1983
(Popularised by Dame Shirley Bassey)