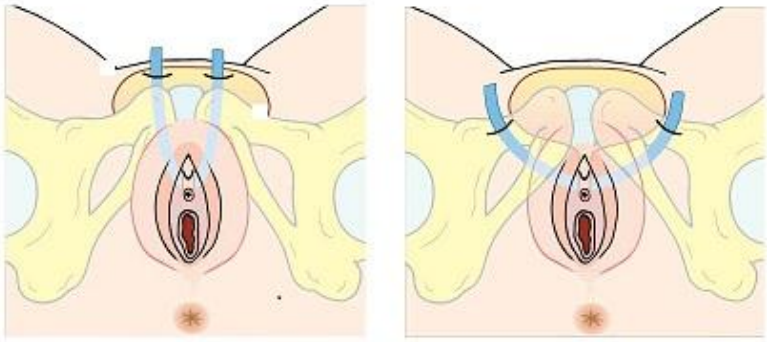
SYDDANSK UNIVERSITET

PhD Thesis

Surgical treatment for urinary incontinence in women

- Danish nationwide cohort studies



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Preface

This PhD study was initiated as a project between Region of Southern Denmark and University of Southern Denmark with the object of identifying regional differences in the quality of care.
The study was conducted in collaboration with the Department of Obstetrics and Gynaecology, Herlev Hospital.

I would like to thank my former main supervisor, Knut Borch-Johnsen, *MD DMSc* for designing the project, securing funding and for his assistance during the initial protocol writing phase.
I would like to express my immense gratitude to Kim Oren Gradel, *DVM, PhD,* who replaced Knut Borch-Johnsen as my main supervisor. Thank you for your conscientious supervision in navigating the world of epidemiological terminology and statistics, your patience, and easy-going and humorous manner.
Further, I would like to thank my co-supervisor Gunnar Lose *MD, DMSc* for scientific and clinical discussions, for sharing his enthusiasm for the field of urogynaecology and for giving me the opportunity to base my studies at Herlev. Many thanks also to my co-supervisor Ulrik Schiøler Kesmodel *MD, PhD* for thorough and critical review of the manuscripts.
Thanks to Arne Poulstrup, former head of the Center of Quality for following the course of my PhD study and continued funding.
I am grateful to the Center for Clinical Epidemiology, in particular to Bente Mertz *MD, DMSc* for letting me be a part of your department and to coordinator Susanne Møllerstrøm for English proof reading of the articles and the thesis.
Thanks to all my colleagues at Runddyssen 13 in Herlev for scientific and non-scientific discussions during lunch and coffee breaks, and their company when travelling to national and international conferences. A special thanks to Ulla Due, *physiotherapis*t, *PhD* to actively share knowledge with all of us and a good advice whenever needed. Also thanks to Cæcilie Krogsgaard Tolstrup, *MD* and Hellen Edwards, *MD* for immensely practical help and support whenever needed.
My thanks to Aase Randtoft, *executive secretary* and Susanne Axelsen, *MD, PhD, associate professor* for admitting me as a board member of The Danish Continence Society. You have firmly impressed upon me that incontinence is not only a scientific discussion but a human concern.
I would like to thank Head of Department Jens Prien-Larsen, *MD* (Dept. of Obstetrics and Gynecology, Nykøbing Falster Hospital) for introducing me to the field of urogynaecology and sharing the interest of urinary incontinence with me.

I owe a special thank-you to my husband, Jens Vej Olesen, for his selfless attitude and loving support throughout my PhD, and to our daughters, Mary and Maj, for being the nicest, funniest and cleverest children ever. Thanks also to my mother, Marianne Steensen Jacobsen, and my parents-in-law, Ellen Vej and Villy Olesen, for their love, unstinting practical help and support.

Copenhagen, September 2016
Margrethe Foss Hansen

Abbreviations

ASA: American Society of Anesthesiologist's Classification
BMI: Body Mass Index
CI: Confidence interval
CPR-number: Civil Registration Number
DHMA: The Danish Health and Medicines Authority
DSOG: The Danish Society of Obstetrics and Gynaecology
DugaBase: The Danish Urogynaecological Database
HR: Hazard ratio
ICD 10: International Classification of Diseases
ICIQ-SF: International Consultation on Incontinence Questionnaire-Short Form
IOQ: Incontinence Outcome Questionnaire
MUI: Mixed urinary incontinence
MUP: Maximum urethral closure pressure
MUS: Midurethral sling
NOMESCO: Danish Nordic Medico-Statistical Committee
OAB: Overactive Bladder Syndrome
PAGH: Polyacrylamide hydrogel
PGI-I: Patient Global Index of Improvement Scale
POP: Pelvic Organ Prolapse
PROMs: Patient reported outcome measures
RCT: Randomized controlled trial
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
SUI: Stress urinary incontinence
TOT: Transobturator tape
TVT: Tension-free vaginal tape
TVT-O: Transobturator tension-free vaginal tape
UI: Urinary incontinence
UIT: Urethral injection therapy
UUI: Urgency urinary incontinence

Definitions conform to the international joint report on the terminology for female pelvic floor dysfunction unless otherwise stated (2).

List of publications

This thesis is based on the following studies:

I: **Reoperation for urinary incontinence: a nationwide cohort study, 1998-2007.**
Foss Hansen M, Lose G, Kesmodel US, Gradel KO: Am J Obstet Gynecol. 2016 Feb;214(2):263.e1-8.doi: 10.1016/j.ajog.2015.08.069. Epub 2015 Sep 5.

II: **Repeat surgery after failed midurethral slings: a nationwide cohort study, 1998-2007.**
Hansen MF, Lose G, Kesmodel US, Gradel KO. Int Urogynecol J. 2015 Dec 28,[Epub ahead of print].

III: **A national population-based cohort study of urethral injection therapy for female stress and mixed urinary incontinence -The Danish Urogynaecological Database, 2007-2011**
Hansen MF, Lose G, Kesmodel US, Gradel KO (Manuscript).

The study was a part of an oral presentation at the 41st Annual Meeting of the International Urogynecological Association (IUGA) in Cape Town, 2-6 August 2016
(Abstract PP31, Int. Urogyn J. Volume 27, Issue 1 Supplement, August 2016)

English Summary

This PhD thesis is based on three original articles. The studies were performed at the Department of Obstetrics and Gynaecology, Herlev University Hospital and at the Center for Clinical Epidemiology, Odense University Hospital.

Urinary incontinence (UI) is a frequent disorder among women, which for the individual can have physical, psychological and social consequences. The current standard of surgical treatment is the synthetic midurethral sling (MUS), which is a minimal invasive procedure.

As the synthetic MUSs (TVT,TVT-O,TOT) were introduced in the late 1990s, there are only a few studies at the long-term follow-up based on nationwide populations; only a few have reported on the risk of reoperation and there is sparse evidence on which treatment should be used subsequently to failure of synthetic MUSs.

Several surgical specialties have documented that department volume, surgeon volume and patient-related factors influence the quality of care. There is little knowledge regarding this in the surgical treatment for UI.

The aims of the thesis were therefore:

1. To describe the five-year incidence of reoperation after different surgical procedures for UI based on a nationwide population over a ten-year period (1998-2007) and to evaluate the influence of department volume (Study I).
2. To describe the choice of repeat surgery after failed synthetic MUSs and the departmental volume for the surgical treatment at reoperation over a ten-year period (1998-2007) based on a nationwide background population (Study II).
3. To evaluate efficacy of urethral injection therapy (UIT) based on patient reported outcome measures (PROMs) and hospital contacts within 30 days for women registered in the Danish Urogynaecological Database (DugaBase) over a five-year period (2007-2011) and the influence of department volume, surgeon volume and patient-related factors (Study III).

Study I: A total of 8671 women were recorded in the Danish National Patient Registry as having undergone surgical treatment for UI from 1998 through 2007.

The lowest rate of reoperation within five years was observed among women who had pubovaginal slings (6%), TVT (6%) and Burch colposuspension (6%) followed TOT (9%), and miscellaneous operations (12%), while the highest observed risk was for UIT (44%). After adjustment for patient´s age, department volume and calendar effect TOT carried a 2-fold higher risk of reoperation (HR, 2.1; 95% CI, 1.5 -2.9) compared with TVT.

Study II: A total of 5820 women had synthetic MUSs at baseline from 1998 through 2007 and were registered in the Danish National Patient Registry and 354 (6%) of these women had a reoperation. The first choice treatment for reoperation was a synthetic MUS and UIT was a frequent second choice. At reoperation, 289 (82%) of the women were treated at the department where they had undergone the primary synthetic MUS. Fewer treatment modalities were in usage and significantly more TOTs were implanted at low volume departments compared to high volume departments.

Study III: A total of 731 women of age 18 or older with first time UITs were registered with first-time UIT in the DugaBase from 2007 through 2011. Logistic regression was used to predict the odds of success pertaining to department volume, surgeon volume and patient-related factors on the Incontinence Questionnaire-Short Form (ICIQ-SF) (frequency of UI, amount of leakage and impact of UI on daily life) and the rate of 30-day hospital contacts.

We applied the definition of "cure" as set out by the steering committee of the DugaBase where a satisfactory result is leakage once a week or less, often or never based on the frequency score and similarly "no leakage at all" based on the frequency score as answering never to leakage.

Among the 252 women who pre- and postoperatively had answered both questionnaires, 75 (29.8%) were cured and 23 (9.1%) achieved no leakage at all at three months follow-up. There was a statistically significant improvement on all three scores of the ICIQ-SF. The mean total ICIQ-SF score was 16.0 (SD 3.8) and after injection at three months follow-up 10.6 (SD 6.2) ($p < 0.001$).

UIT was performed at 16 departments, of which four high volume departments performed 547 of 814 UITs (67.2%). The risk of hospital contacts was lower for women treated at a high volume department (adjusted OR 0.27; 95% CI 0.09-0.76).Women treated by a high volume surgeon (> 75 UITs during the career as a surgeon) had a higher chance of cure on the frequency score than the low volume surgeon (≤ 25 UITs) (adjusted OR 4.51; 95% CI, 1.21-16.82) and a lower risk of 30-day hospital contacts (adjusted OR 0.35; 95% CI, 0.16-0.79). Women with severe UI had less

likelihood of cure in all ICIQ-SF scores. A preoperative use of antimuscarinic drugs lowered the chance of cure on the frequency (adjusted OR 0.14; 95%, CI 0.04-0.41) and the amount score (adjusted OR 0.33; 95%, CI 0.13-0.82).

Conclusions

Study I: The study provided physicians with a representative evaluation of the rate of reoperations after different surgical procedures for UI. The observation that TOT was associated with a significantly higher risk of reoperation than TVT is novel in the literature and has important implications for both surgeons and patients when they consider surgical options for UI.

Study II: The majority of women had reoperation at the same department as the primary synthetic MUS. Fewer treatment modalities were in use at low volume departments compared with high volume departments. It seems appropriate in the absence of evidence for the best treatment after failed synthetic MUSs, that women are referred to highly specialized departments for diagnosing and treatment.

Study III: This national population-based cohort study represented cure among women who had UIT in an everyday life setting. Results seemed to be in the lower end of the spectrum compared to the literature.A learning curve for UIT indicated that the treatment should be restricted to fewer hands to improve the surgical education and consequently be a success for women with UIT. The severity of UI was a strong predictor for a lower degree of cure. Similarly, the use of antimuscarinic drug preoperatively decreased the likelihood of cure indicating that women with severe MUI or UUI also have less chance of cure.

Dansk resume

Denne ph.d.-afhandling er baseret på tre original-artikler. Arbejdet blev udført på Gynækologisk-Obstetrisk afdeling, Herlev Hospital, og på Center for Klinisk Epidemiologi, Odense Universitetshospital.

Urininkontinens er en hyppig lidelse blandt kvinder, som for den enkelte kan have fysiske, psykiske og sociale konsekvenser. Inden for den kirurgiske behandling af urininkontinens er standarden i dag midt-urethral slyngekirurgi, som er minimal invasiv kirurgi.

Da de midt-urethrale slynger (TVT, TVT-O, TOT), blev indført i slutningen af 1990erne, er antallet af studier med langtidsopfølgning på nationalt plan begrænset; kun få har rapporteret risiko for reoperation og hvilken behandling, der efterfølgende bør anvendes, er kun sparsomt belyst.

Det er inden for flere kirurgiske specialer blevet dokumenteret, at afdelingsvolumen, kirurgvolumen og patientrelaterede faktorer påvirker kvaliteten. Der er begrænset med viden inden for den kirurgiske behandling af urininkontinens.

Formålet med afhandlingen var derfor:

1 At beskrive hyppighed af reoperation inden for 5 år efter kirurgisk behandling for urininkontinens baseret på en national population over en 10-års periode (1998-2007) og at vurdere betydningen af afdelingsvolumen (Studie I).
2. At beskrive valg af behandlingsmetoder efter fejlslagen midt-urethral slyngekirurgi og afdelingsvolumen ved reoperation over en 10-års periode (1998-2007) baseret på en national population (Studie II).
3. At vurdere effekten af urethral injektions-behandling baseret på PROMs (Patient Reported Outcome Measures) og hospitalskontakter inden for 30 dage for kvinder registeret i Dansk Urogynækologisk Database (DugaBase) over en 5-års periode samt betydningen af afdelingsvolumen, kirurgvolumen og patient-relaterede faktorer (Studie III).

Studie I: I alt 8671 kvinder var registeret i Landspatientregisteret med kirurgisk behandling for urininkontinens fra 1998 til 2007.
Den laveste rate af reoperation inden for 5 år blev observeret blandt kvinder, som fik pubovaginale slynger (6%), TVT (6%) og Burch kolposuspension (6%) efterfulgt af TOT (9%) og diverse operationer (12 %), hvorimod den højest observerede risiko var for urethral injektions-behandling

(44%). Efter justering for patientens alder, afdelingsvolumen og kalendertid var TOT forbundet med en 2 gange højere risiko for reoperation (HR 2,1; 95 %, CI 1,5-2,9) sammenlignet med TVT.

Studie II: I alt 5820 kvinder fik foretaget midt-urethral slyngekirurgi fra 1998 til 2007 og var registreret i Landspatientregistret. Heraf fik 354 (6 %) foretaget en reoperation. Førstevalgsbehandling ved reoperation var en midt-urethral slynge, og urethral injektions-behandling var et hyppigt andetvalg. Ved reoperation blev 289 (82 %) af kvinderne behandlet på afdelingen, hvor de havde fået foretaget den primære midt-urethrale slynge. Der blev anvendt færre behandlingsmuligheder ved reoperation og anlagt signifikant flere TOTer på lavvolumen-afdelinger i forhold til højvolumen-afdelinger.

Studie III: Kohorten omfattede kvinder i alderen 18 år eller ældre som var registreret med førstegangs urethral injektions-behandling i DugaBase fra 2007 til 2011. Logistisk regression blev anvendt til at prædiktere succes af behandling i forhold til afdelingsvolumen, kirurgvolumen og patient-relaterede faktorer på Incontinence Questionnaire-Short Form (ICIQ-SF) (hyppighed af urininkontinens, mængde af urininkontinens og påvirkning af dagligdag) og hyppighed af hospital kontakter inden for 30 dage.

Vi anvendte definitionen af "helbredelse" fastsat af DugaBasens styregruppe, hvor et tilfredsstillende resultat er baseret på frequency scoren som lækage max. en gang om ugen eller mindre (3) og ligeledes "ingen lækage" også baseret på frequency scoren som svaret 'aldrig' til spørgsmålet om lækage.

Blandt de 252 kvinder, som præ- og postoperativt havde besvaret begge spørgeskemaer, var 75 (29.8 %) kvinder helbredt og 23 (9,1 %) havde ingen lækage ved 3 måneders opfølgning. Der var en statistisk signifikant forbedring på alle tre scorer i ICIQ-SF. Den gennemsnitlige totale ICIQ-SF score var 16,0 (SD 3,8) og efter injektion ved 3 måneders opfølgning 10,6 (SD 6,2) ($p < 0,001$).

Urethral injektions-behandling blev udført på 16 afdelinger, hvoraf fire højvolumen-afdelinger udførte i alt 547 af 814 urethrale injektions-behandlinger (67,2 %). Der var lavere risiko for hospitalskontakter inden for 30 dage for kvinder behandlet på en højvolumen-afdeling (adjusted OR 0.27; 95% CI 0.09-0.76). Kvinder behandlet af en højvolumen-kirurg (>75 urethrale injektions-behandlinger som kirurg) havde større chance for helbredelse målt på hyppighed af urininkontinens på ICIQ-SF i forhold til kvinder behandlet af en lavvolumen-kirurg (≤ 25 urethrale injektions-

behandlinger) (adjusted OR 4.51; 95% CI, 1.21-16.82) og lavere risiko for hospitalskontakter inden for 30 dage (adjusted OR 0.35; 95% CI, 0.16-0.79). Kvinder med svær urininkontinens havde mindre sandsynlighed for helbredelse målt på alle ICIQ-SF scorer. Et forbrug af antimuskarinergika præoperativt mindskede chancerne for helbredelse målt på hyppighed (adjusted OR 0.14; 95%,CI 0.04-0.41) og mængde af urin på ICIQ-SF (adjusted OR 0.33; 95%, CI 0.13-0.82).

Konklusioner

Studie I: Studiet bidrager med en repræsentativ vurdering af risiko for reoperation efter forskellige kirurgiske procedurer for urininkontinens. Observationen, at TOT er forbundet med dobbelt så høj risiko for reoperation i forhold til TVT, er ny i litteraturen. Den forhøjede risiko for reoperation efter TOT er vigtig at medinddrage for såvel læger som patienter, når de overvejer metoder til behandling af urininkontinens

Studie II: Størstedelen af kvinderne fik foretaget reoperation på samme afdeling som den primære midt-urethrale slynge. Færre behandlingsmuligheder var i anvendelse på lavvolumen afdelinger sammenlignet med højvolumen afdelinger. Det synes passende at kvinder med fejlslagen slynge henvises til en højtspecialiseret afdeling mhp. videre udredning og behandling, da evidensen på området er sparsom.

Studie III: Dette nationalt baserede studie repræsenterede helbredelse blandt kvinder, som fik foretaget urethral injektions-behandling i daglig praksis. Resultaterne synes at være i den lavere ende af spektret sammenlignet med litteraturen. Det blev antydet, at der er en indlæringskurve for urethral injektions-behandling og at behandlingen bør samles på færre hænder for at forbedre den kirurgiske uddannelse og dermed også chancen for helbredelse. Sværhedsgrad af urininkontinens var en stærk prædiktor for lavere helbredelse. Det samme gjaldt et forbrug af antimuskarinergika præoperativt, hvilket indikerer, at kvinder med svær MUI eller UUI har mindre sandsynlighed for helbredelse.

1. Introduction

1.1 Background

Urinary incontinence (UI) is defined as the complaint of involuntarily loss of urine (4). Although not life threatening, this condition can have physical, psychological and social consequences for the individual (5, 6). The prevalence of female UI is estimated as being 10-40%, depending on how the population is defined and wider ranges can be found among elderly women (7). Among a Danish cohort of women aged 40-60 years, the prevalence of one involuntarily leakage *per* week has been estimated as 16% (8). The need for treatment is expected to increase in the future as a combined result of a still increase in the population of persons aged 65+ (9) and better treatment modalities (7).

The most frequent type of UI is stress urinary incontinence (SUI)(50%), followed by mixed UI (MUI)(36%) and pure urgency UI (UUI)(11%) (10). SUI is defined as an involuntary loss of urine on effort, physical exertion, sneezing or coughing, and UUI as a complaint of involuntary loss of urine associated with urgency (2). MUI includes stress and urgency components. A variety of treatments exists for UI, ranging from conservative (pelvic floor muscle training, bladder training, lifestyle changes), through pharmacological and mechanical (intravaginal devices) to surgery. Surgery is predominantly used in women with SUI and to some extent in women with MUI (7).

1.2 Surgical treatment for urinary incontinence

The current standard surgical intervention is the synthetic midurethral sling (MUS) (11), which is a tape made of polypropylene placed mid-urethra under tension (7).

The synthetic MUS was introduced in the late 1990s and rapidly replaced colposuspension and pubovaginal slings as the current standard due to the advantages of technical ease, shorter operative time and feasibility as an outpatient procedure (12).

The tension-free vaginal tape (TVT) was the first synthetic MUS and has shown objective and subjective cure rates of 85% (13, 14). The transobturator tapes (TVT-O, TOT) were introduced to minimize the surgical complications of TVT, which included injury to the bladder, major vessels and bowel (11). The efficacy is similar for both synthetic MUSs at short and mid-term follow-ups (15-18). Several modifications of the synthetic MUSs have subsequently been introduced, but without clinical data on their safety and efficacy (7).

Urethral injection therapy (UIT) is less minimal invasive than the synthetic MUSs and adverse events are fewer and more mild and moderate (19, 20), but as the efficacy is lower (19, 20) it is often used as a second line approach (11).

1.3 Department volume, surgeon volume and patient-related factors

It has been documented across several surgical specialities that department and surgeon volume and patient-related factors influence the quality of care (21, 22). Influence of these factors on the surgical treatment for UI have previously been investigated in Danish studies (23-26) but have only been sparsely studied internationally.

The department volume reflects organizational characteristics (*e.g*. the skills of the clinical team, the availability of medical and technical in-service teaching status), whereas the surgeon volume reflects individual skills (technical skills and quality of decision-making) (27). The association between department and surgeon volume and quality of care has generally been demonstrated as being positive or neutral, and never negative (28). The most complex procedures tend to have the strongest volume-outcome association (27).

Although both department volume and surgeon volume are assumed to affect the outcome, their relative contributions have not been established (27). Crucial for the understanding of the volume-outcome relationship is that there is not *a priori* a positive correlation between department and surgeon volume (22). A high volume department might accrue a large number of low volume surgeons, whereas a low volume department might have one surgeon who performs all instances of a given procedure. It is therefore important that studies interpreting the results of department volume also take account of the individual surgeon volume (21). Differences in patient-related factors in the relationship (such as age, comorbidity and lifestyle-related factors) between high and low volume might bias the surgical outcome (22, 28).

1.4 Organization of the surgical treatment for urinary incontinence in Denmark

There is generally sparse literature on the influence of the volume-outcome association on the surgical treatment for UI among women. The influence of surgeon volume on the synthetic MUS procedure has to some extent been documented, notably with reference to the risk of bladder perforation (29-31), but also in terms of lowering the risk of complications (32) and achieving better subjective outcomes (24, 33). Aspects of the department volume and how to achieve adequate surgeon volume, however, have received little attention in studies to date.

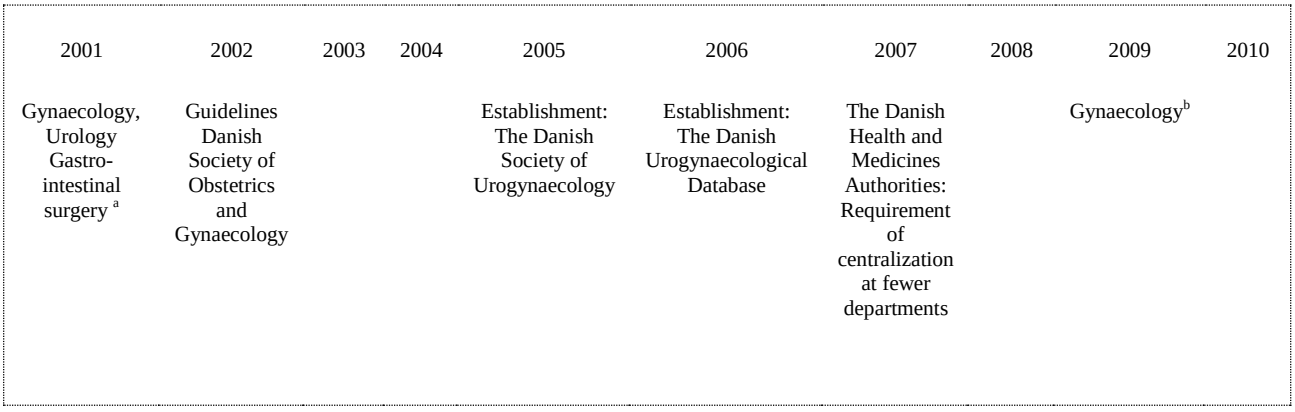
Internationally, Denmark is one of the countries with the most systematic monitoring of the quality of care (34). It is therefore natural for department volume, surgeon volume and patient volume to have been addressed as important issues within the surgical treatment for UI (23-26, 35, 36).

Throughout the period 2001 to 2009, the surgical treatment for female UI underwent centralization in Denmark; from being distributed across three specialties (gynaecology, urology and gastro-intestinal surgery) it was largely lodged with a single specialty (gynaecology) (35, 36). Many different procedures *per* department were in usage in 2001, but were reduced by the end of 2009 (35, 36).

However, a substantial variation in the assessment and surgical treatment for UI at the respective departments persisted (36) despite the fact that national guidelines for the treatment of UI had been put in place (36).

A Danish PhD thesis demonstrated that, based on the Danish National Patient Registry and questionnaires completed by hospital departments and patients, both department and surgeon volume affected the surgical quality of synthetic MUSs (24-26). Partly in recognition of this, the Danish Health and Medicines Authority (DHMA) introduced requirements for department volume (37) and in the year 2010 further centralization within the specialty of Gynaecology was established (38).

Figure 1 Development of surgical treatment for urinary incontinence in women



[a] Surgical treatment for urinary incontinence in women was performed within the three specialties, Gynaecology, Urology and Gastro-intestinal surgery.

[b] Surgical treatment for urinary incontinence in women was performed within the specialty Gynaecology.

1.5 Establishment of the Danish Urogynaecological Database

In several countries, clinical databases were established in the beginning of the millennium to enhance the surgical quality of urogynaecology (Norway 1998) (Netherlands 2000) (United Kingdom 2000) (Austria 2000, closed) (Denmark 2006) (33, 39-42). The main purpose was to document the quality of new techniques and to stimulate a clinical and scientific interest in urogynaecology. The databases were initiated voluntarily by working groups of urogynaecologists (33, 39, 40, 42), but have now become more established as financed by the government (33, 39, 40, 42).The DugaBase, however, is the only database that it is mandatory by law to report to (42)*(Personal comment: Rune Svenningsen, Steven Schraffordt, Jonathan Duckett, Thomas Aigmueller)*.

The Danish Urogynaecological Database (DugaBase) was established in 2006 (42).

The database completeness is high, whereas the data completeness during all years has been lower. Clinically, the DugaBase is used to compare local data on the surgical treatment with the national mean values and departments, who deviate considerably, are informed in order to alter their treatment provision. Scientifically, the DugaBase holds the advantage of including multiple patient-related data and objective and subjective outcomes based on a national population (42-45).

The quality indicators and standards for UI and pelvic organ prolapse (POP) are developed by the DugaBase steering committee based on the available evidence (Appendix 1). The quality indicators for UI include waiting time, subjective assessment of success after surgical treatment for UI, the need for further treatment and recent reoperations after synthetic MUS within two and five years was implemented.

In this PhD thesis, the quality of surgical treatment for UI was assessed with reference to some of the quality indicators in the DugaBase.

1.6 Reoperation for urinary incontinence

The risk of reoperation after surgical treatment for UI based on national populations has not been established internationally (12, 46, 47). Existing literature specifies an overall lifetime rate of reoperation of about 8-9% after an initial operation for UI (12). There are, however, conflicting statements about the risk of reoperation after specific surgical procedures for UI. Only a few register-based studies have reported on the risk of reoperation after TVT at long-term follow-up (5 - 10 years) (14, 48, 49). The risk of reoperation after TVT based on a nationwide population has remained relatively unknown and, similarly, no national comparative studies on the risk of reoperation after TVT and TOT have been conducted.

1.7 Repeat surgery after failed midurethral slings

The current literature indicates that a small proportion of women will require a second procedure after failure of a synthetic MUS (50, 51).There is, however, no consensus on which treatment should be used (50, 52, 53). The literature indicates that synthetic MUSs represent the leading treatment option for repeat surgery, but the results are limited to short-term follow-up (54). A variety of surgical treatments exists, but there is little data to support their use (50, 54). A few nationwide cohort studies have reported on repeat surgery after the failure of synthetic MUSs. As there is currently little knowledge regarding which procedures are used, it is difficult to assess and discuss which procedures should be used after the failure of synthetic MUSs (50).

1.8 Urethral injection therapy for stress and mixed urinary incontinence

UIT has been performed since the early 20th century (55) and a variety of agents have been launched, but several of these were retracted due to product related side effects (20). It is an attractive alternative to synthetic MUSs due to its few and mild side effects (56). Polyacrylamide hydrogel **(**PAGH) was introduced in Europe as a bulking agent in 2006 and is now widely used (57, 58). The current knowledge on PAGH is based on ten studies with a follow-up period of one to three years (23, 59-67). However, no national population-based studies of PAGH have been conducted and there is a lack of studies representing patients in the daily clinic (58).

2. Aims

The aims of the thesis were to evaluate the surgical treatment for UI based on national populations and the influence of department volume, surgeon volume and patient-related factors:

1. To describe the five-year incidence of reoperation after different surgical procedures for UI based on a nationwide population over a ten-year period (1998-2007) and to evaluate the influence of department volume (Study I).

2. To describe the choice of repeat surgery after failed synthetic MUSs and department volume for surgical treatment at reoperation over a ten-year period (1998-2007) based on a nationwide background population (Study II).

3. To evaluate the efficacy of urethral injection therapy (UIT) based on patient reported outcome measures (PROMs) and hospital contacts within 30 days for women registered in the Danish Urogynaecological Database (DugaBase) over a five-year period (2007-2011) and the influence of department volume, surgeon volume and patient-related factors (Study III).

3. Materials and methods

3.1 Study setting

All studies included women who had surgical treatment for UI in Denmark.
The healthcare system in Denmark is financed by tax and provides care free of charge for the individual patient. The initial contact is with the general practitioner, who may refer the patient to a public or private hospital (68, 69). Denmark has approximately 5.5 million inhabitants and consists of five regions.

3.2 Source of data

All Danish residents are assigned a unique Civil Registration Number (CPR-number), which enables linkage between all nationwide registries (70). The following data sources have been used in this thesis:

The Danish Civil Registration System (Studies I, III)

The Danish Civil Registration System was established in 1968 and provides information on gender, date of birth and continuously updated data on vital status (70).

The Danish National Patient Registry (Studies I, II, III)

The Danish National Patient Registry was established in 1977 and provides information on diagnoses, minor procedures, and operations in Danish hospitals (68, 69). It is mandatory by law for all hospital departments and private hospitals to report to the Danish National Patient Registry.
The registry is used for administration, quality of care, and research and studies of procedure codes within the Danish National Patient Registry have shown to have a high validity (71).

The Danish Urogynaecological Database (Study III)

The Danish Urogynaecological Database (DugaBase) was established in 2006 to monitor, ensure and improve the quality of urogynaecological surgery (42, 43). It is mandatory by law for all hospital departments and private hospitals to report to the DugaBase (42).
The database contains information on women residing in Denmark at the age of 18 or older who have had surgical treatment for UI or POP. The DugaBase is organized with a steering committee, consisting of specialist within Obstetrics and Gynecology, administrative employees from the

Region of Southern Denmark and the Center of Epidemiology (3, 42), a project manager and a secretary. Public and private hospital departments report data by a web-based module.
The DugaBase contains information on the operative course: 1) A preoperative patient questionnaire on baseline information and PROMs, 2) A questionnaire completed by the gynecologist including a preoperative examination, 3) A questionnaire on the surgical procedure performed (*e.g.* procedure code, surgeon volume, use of antibiotic prophylaxis), 4) A postoperative patient questionnaire including the same PROMs as preoperatively, possible complications and reoperations, and 5) Postoperative follow-up questionnaire for health care professionals.
In the DugaBase PROMs are based on the validated Incontinence Questionnaire-Short Form (ICIQ-SF), which in 2013 was supplemented with the Patient's Global Impression of Improvement (PGI-I score) postoperatively (44). The ICIQ-SF has been translated into, but not validated in, Danish (43) and consists of three questionnaires (frequency of UI, amount of leakage, and impact of UI on daily life).
The database completeness of the DugaBase has increased from 33% for UI in 2007 to 93% in 2011 using the Danish National Patient Registry as reference (3, 42). The database completeness has remained as high as 92.6 % for surgical treatment for UI in 2014 (72). During the years 2007-2011 the data completeness has constantly been lower and was in 2014 52.7% (72). This is mainly due to the fact that the departments have a heterogeneous way of follow-up after surgical treatment for UI as some departments routinely follow-up all patients whereas other departments only follow up on complicated patients (42).
The validity of eleven main variables has been examined (date of surgery, department, procedure code antibiotic prophylaxis, prior surgery for UI and POP, prior hysterectomy, height, weight, parity and smoking), and an agreement of 90-100% was found when comparing information from the database with medical records (42).

The Register of Medicinal Products Statistics (Study III)

The Register of Medicinal Product Statistics was established in 1993, and retrieves information on prescriptions from all Danish pharmacies and is maintained by Statistics Denmark (73). Only a few studies have therefore assessed the completeness and validity of this register (74, 75). There are, however, factors which point towards a high data quality (73). The Register of Medicinal Product Statistics constitutes an integral part of the pharmacist´s key function of selling prescription drugs, which includes maintaining the computerized reimbursement account (73). The universal

reimbursement system thus provides a strong economic incentive for recording all drugs dispensed. All drug- packets are labelled with an optically scanned barcode that acts as linkage to other registers (73).

3.3 Study I

The study population comprised all women registered in the Danish National Patient Registry with surgical treatment for UI from 1998 through 2007, and no surgery two years prior to enrolment in the study (Fig.2). To evaluate the cumulative risk of reoperation within five years, we used the NOMESCO procedure codes for all operations (76). The procedure codes were divided into six groups (Appendix 2) 1) TVT ("KLEG10"), 2) TOT ("KLEG10A"), 3) UIT ("KKDV20" "KKDV22") with polyacrylamide gel or polyacryl hydrogel 4)"Pubovaginal slings ("KKDG30") which is an a.m. McGuire procedure performed with autologous fascia (rectus fascia or fascia lata). 5) Burch colposuspension ("KDG00") and 6) Miscellaneous operations which separately were less frequently used procedures for UI ("KDG01", "KDG10", "KDG31", "KDG40", "KDG50", "KDG96","KDG97","KLEG00","KLEG20",and"KLEG96"). We registered a reoperation defined as any subsequent surgical treatment for UI using the same procedure codes.

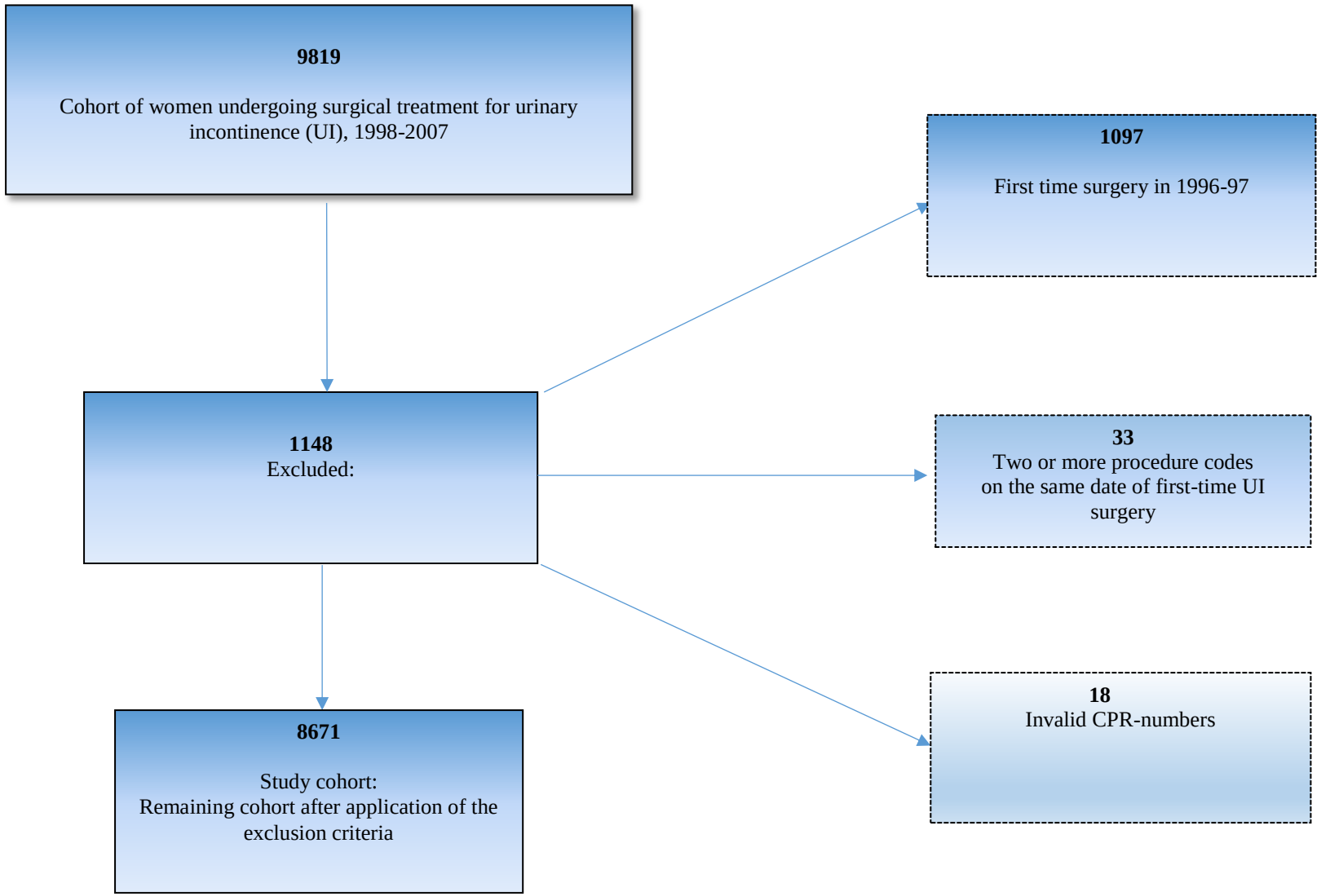
3.4 Study II

The study population consisted of women registered in the Danish National Patient Registry who had a synthetic MUS ("KLEG10") ("KLEG10A") from 1998 through 2007 at baseline. We described the choice of repeat surgery within a five-year period and department volume at the primary procedure and at reoperation.

In studies both I and II department volume was calculated as the annual number of the total UI procedures for each department and computed to an index for the ten-year study period from which the final tertiles (low, medium, and high volume departments) were computed.

A highly specialized department was defined as one of the largest departments in each region in Denmark (equivalent to the five largest university hospitals).

Figure 2 Derivation of study cohort (Study 1)



3.5 Study III

The study population included women 18 years or older residing in Denmark who had a first-time injection with PAGH from 2007 through 2011, as registered in the DugaBase. To assess that a UIT in 2007 was likely to be the woman's first-time injection we included 2006 as a lag year to ensure that no women had UIT one year prior to enrollment. Only women, who had completed the questionnaires pre-and postoperatively were included in the main analyses (Fig.3). The guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) were applied (77).

The primary outcomes were based on the ICIQ-SF, completed at three months follow-up after the primary UIT and a secondary outcome was hospital contacts within 30 days from the primary procedure.

The ICIQ-SF consists of three questions (frequency of UI, amount of leakage, and impact of UI on daily life) as well as the sum based on these questions (total ICIQ-SF) (Appendix 3).

Within each of the three questions "cure" was based on a dichotomization in accordance with globally accepted criteria reported previously (3, 23, 59-62, 66) .

The steering committee of the DugaBase has defined "cure" (subjective patient assessment of success) as leakage once a week or less often or never based on the frequency score and we focused in particular on this outcome (3) and on "no leakage at all " defined on the frequency score as answering never to leakage of urine (59). "Change" was evaluated as the difference on the ICIQ-SF total pre-and postoperatively.

All relevant hospital contacts, within 30 days from the primary procedure, to a department of obstetrics and gynaecology with a diagnosis classified according to the International Classification of Diseases, tenth edition (ICD 10)(Appendix 4) were identified (78) .

Department volume was defined as in a previous study, high (≥15 UITs *per* year) and low (<15 *per* year) (23). The Danish National Patient Registry was used as gold standard to secure that the classification of department volume was based on the actual annual number of UITs. 814 of 1346 UITs were registered in the DugaBase and 16 of 22 departments were registered in the DugaBase. The remaining six departments not registered in the DugaBase contributed with 61 of the 1346 (4.5%) of the UITs. All four high volume departments were registered in both the DugaBase and

the Danish National Patient Registry. The high volume departments registered in the DugaBase performed 547 of the 814 UITs (67.2%).

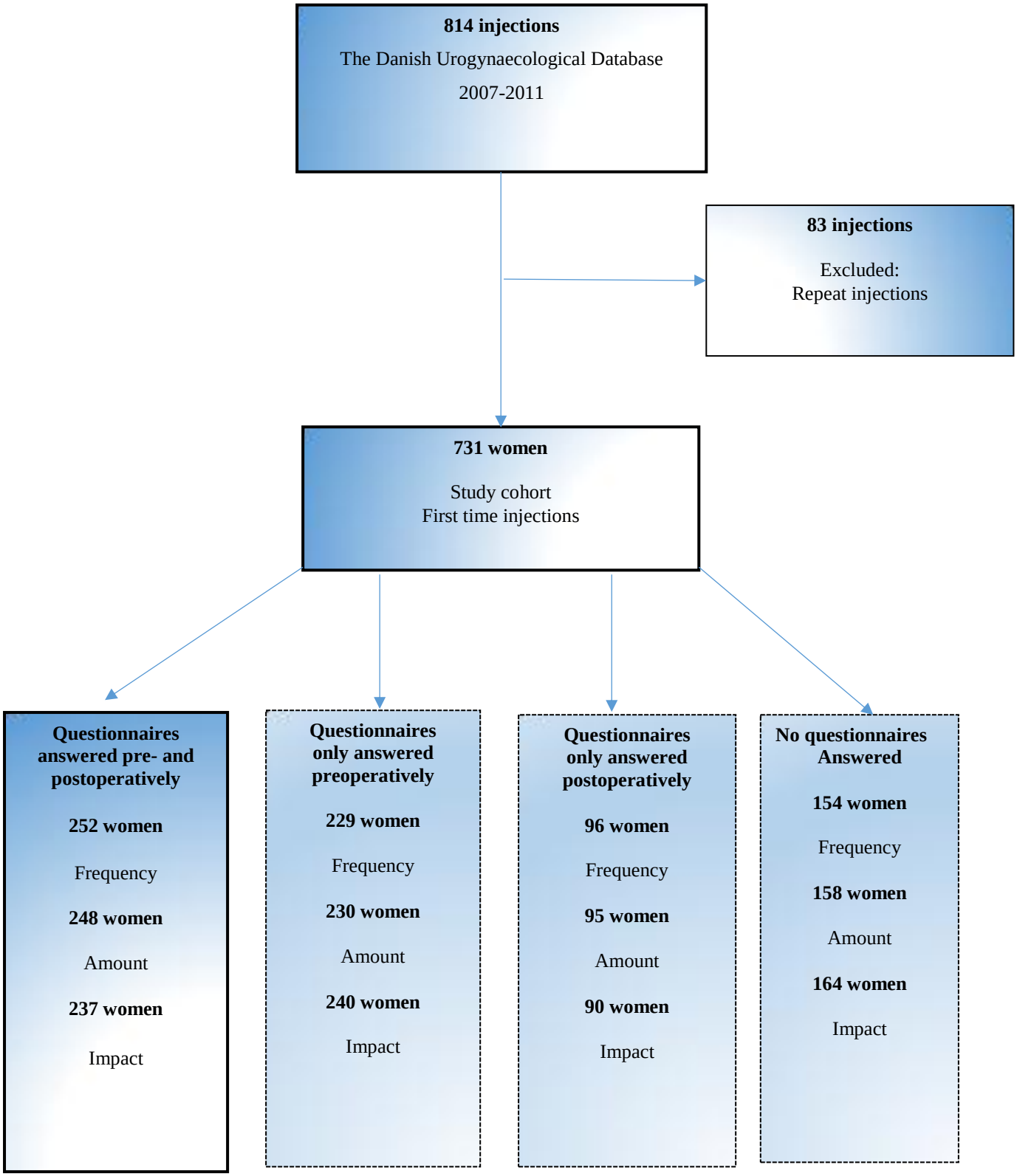
The high volume departments were registered in the Danish National Patient Registry with 874 of the total 1346 UITs (64.9%). The high volume departments performed 43.7 procedures on average *per* year whereas the low volume departments on average performed 3.6 procedures *per* year. There was a decreasing usage of UITs, from annually 354 in 2007 to 170 UITs in 2011.

Surgeon volume as registered in the DugaBase was categorized into three groups of surgeon volume (number of injections performed during the career as a surgeon), low (< 25), medium (26-75) and high volume (>75).

Patient-related factors included a medical history as registered in the DugaBase (age, body mass index (BMI), American Society of Anesthesiologist's (ASA) Classification, previous surgery (hysterectomy, UI surgery, POP surgery) and severity of UI preoperatively using the ICIQ-SF). Information on preoperative use of medication related to UI was retrieved from The Register of Medicinal Product Statistics (diuretics (ATC C03) antimuscarinic drugs (ATC G04BD), oestrogens (ATC G03C) and a group of less frequently used drugs (desmopressin ATC H01BA02, imipramine ATC N06AA02 and duloxetine ATC N06AX21)).

Figure 3 Description of the study cohort (Study II)

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)



3.6 Statistical analyses

Data analysis in study I, II was performed using Stata version 13.0 (StataCorp, College Station, TX, USA) and study III using STATA version 14.0 (StataCorp, College Station, TX USA).

Study I: Women with or without reoperation were compared by the χ^2-test and the χ^2-test for trend (categorical variables) or the Student's t-test (age). The starting date was set at baseline surgery and an outcome was a reoperation within the following five years. A Kaplan Meier curve was used for measuring the time to reoperation for the six groups of surgical treatment. Information on the vital status was obtained using the CPR-number, and data were censored before time if the women disappeared, emigrated or died within the five-year follow-up period.
A Cox proportional regression hazard model assessed the hazard ratio (HR) with 95% confidence intervals (CIs) for reoperation for each type of procedure (TVT as reference group), adjusting for the patient's age, department volume, and calendar effect.

Study II: Descriptive statistics were used to characterize the women undergoing synthetic MUSs at baseline and to evaluate the treatment modality and the departmental volume at the primary operation and reoperation. Women with or without reoperation were compared by the χ^2-test (categorical variables) or the Student´s t-test (continuous variables). To evaluate the department volume (low, medium, high) for the reoperations we used the χ^2-test for trend.

Study III: The first time injection was the analytical unit. Descriptive statistics was used to evaluate the baseline characteristics and outcomes. To evaluate the baseline characteristics between patients treated by a low, medium or high surgeon volume, we used the χ^2-test for trend (categorical variables) and one way analysis of variance (ANOVA) (continuous variables) and for department volume the χ^2-test (categorical variables) and the Student´s t-test (continuous variables). Any change from baseline in the ICIQ-SF -scores was analysed by the Wilcoxon signed-rank test.
In logistic regression, the ICIQ-SF postoperatively was dichotomized for all three questionnaires (Appendix 3) and adjusted by the preoperative ICIQ-SF score ("severity"). We analysed the significance of department and surgeon volume and patient-related factors believed to be clinically relevant by uni- and multivariate logistic regression. Hosmer Lemeshow goodness-of-fit test was calculated to assess the fit of the models.

We adjusted for the following variables believed to be clinically relevant: Age (continuous), BMI (continuous), ASA Classification (reference 1-2 (reference), yes), parity (continuous) previous hysterectomy (no (reference), yes), previous UI surgery (no (reference), yes), previous POP surgery

(no (reference), yes), use of oestrogen preoperatively (no (reference), yes), use of antimuscarinic drugs preoperatively (no (reference), yes), and use of diuretics preoperatively (no (reference),yes).

In sensitivity analyses, we compared baseline patient characteristics, severity of UI, department volume and surgeon volume between women who had filled in both questionnaires pre- and postoperatively and women who had not completed the questionnaires and similarly for women who had completed both questionnaires *vs.* women who only filled in the questionnaire pre-or postoperatively. A p-value < 0.05 was considered statistically significant.

3.7 Ethics and approvals

The studies of this thesis were approved by the Danish Data Protection Agency; Studies I, II: J.nr 2013-41-2210, Study III: J.nr. 2012-41-0414 and Study IV: j.nr.2013-41-1813.
None of the studies needed approval from the Health Research Ethics Committee (http://www.dnvk.dk/CVK/Home/English.aspx) as they were register-based studies.

4. Main results

4.1 Study I

A total of 8671 women (56.1 years, ± 12.6) underwent surgical treatment for UI from 1998 through 2007. Among these, 888 women (10%) were reoperated within a five-year period. The lowest rate of reoperation was observed among women who had pubovaginal slings (6%), TVT (6%) and Burch colposuspension (6%) followed by TOT (9%), and miscellaneous operations (12%), while the highest observed risk was for UIT (44%). For UIT most of these repeat surgeries were reinjections as a total of 379 women had repeat surgery and among these, 238 (62.7%) were reinjections.

At baseline, women subsequently undergoing reoperation were significantly older than women not having a reoperation (58.4 *vs.* 55.9 years, $p < 0.001$). However, the difference was only present for women operated with TOT (58.3 *vs.*53.8 years, $p < 0.004$) and UIT (64.4 *vs.* 61.7 years, $p < 0.009$).

The number of women who underwent reoperation was significantly increasing from low volume (6%) over medium volume (8%) to high volume departments (12%) (P for trend < 0.001).

We stratified this by the six groups of surgical treatments, and only women with UIT had a higher frequency of reoperation increasing with department volume *e.g.* women with UIT were to a higher extent from high volume departments *vs.* low volume departments (86.5% *vs.* 0.8%, $p < 0.06$). No differences were observed for the other treatment modalities.

In the first period (1998-2002) the proportion of TVTs (35%) was almost equal to Burch colposuspensions (28%), but in the second period (2003-2007) the synthetic MUSs had replaced Burch colposuspension in the surgical treatment for UI (81% vs. 2%, Table 1). At low volume departments, TOT (29%) was more frequently used compared to high volume departments (13%), whereas UIT was more rarely used.

Table 1 Surgical procedures for urinary incontinence and department volume, 1998-2002 and 2003-2007

	Period 1998-2002				Period 2003-2007			
Department Volume (%)	Low (n = 221)	Medium (n = 519)	High (n = 1820)	Total (n = 2560)	Low (n = 424)	Medium (n = 1576)	High (n = 4111)	Total (n = 6111)
TVT (%)	56 (25)	102 (20)	73(40)	889 (35)	289 (68)	1178 (75)	2674 (65)	414 (68)
TOT (%)	-	-	-	-	122 (29)	149 (10)	519 (13)	790 (13)
UIT (%)	4 (2)	3 (1)	129 (7)	136 (5)	4 (1)	132 (8)	607 (15)	743 (12)
Colposuspension (%)	116 (53)	240 (46)	372 (20)	728 (28)	1 (0)	46 (3)	56 (1)	103 (2)
Pubovaginal slings (%)	1 (1)	55 (11)	178 (10)	234 (9)	0 (0)	57 (4)	110 (3)	167 (3)
Miscellaneous (%)	44 (20)	119 (23)	410 (23)	573 (22)	8 (2)	14 (1)	145 (4)	167 (3)

TVT Tension- free vaginal tape TOT Transobturator tape UIT Urethral injection therapy

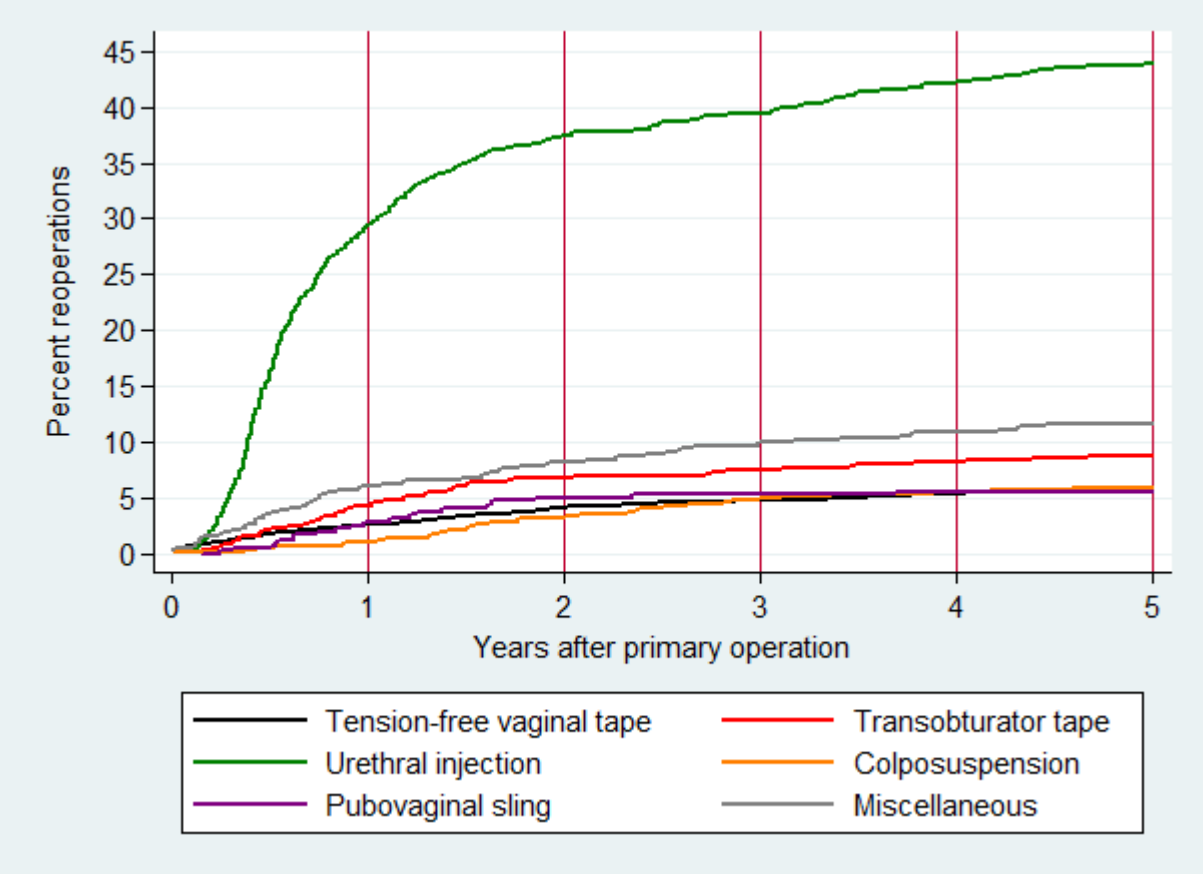
Blank cells: Transobturator tape was first implemented in 2003 in Denmark and therefore no data appear in these cells (1998-2003)

The risk of reoperation was determined by the Kaplan-Meier curves for the six groups of treatments (Fig.4). The majority of reoperations occurred within the first two years of the primary operation and then levelled off during the remaining three years. The median time to reoperation was one year for sling surgery (TVT, TOT and pubovaginal slings), two years for Burch colposuspension, and six months for UIT.

Among women with UIT, 30% had repeat UI surgery within the first year and 14% had repeat UI surgery within the first to five years.

Figure 4 Kaplan-Meier survival curve after surgical treatment for urinary incontinence at baseline

This survival curve depicts the cumulative incidence of reoperation after six surgical procedures for urinary incontinence. The table lists the cumulative incidence of reoperation after data were censored for death, emigration, and disappearance at years 1, 2, 3, 4 and 5.



As four women emigrated before their primary operation 8667 women were included in the Cox proportional hazard model. A total of 368 women (4%) were censored before time due to death (345), emigration (22), or disappearance (1).

After adjusting for age, department volume, and calendar effect the risk of repeat surgery was almost 12-fold higher for UIT and for TOT the risk of reoperation was significantly higher in comparison to TVT (HR, 2.1;95% CI 1.5-2.9) (Table 2). There was virtually no difference between the crude and adjusted HRs.

Table 2 Cox proportional hazard regression analysis for time to repeat urinary incontinence surgery

	Hazard ratio (95%; CI), Reoperation	Adjusted Hazard ratio (95%; CI), reoperation [a]
TVT	(Reference)	(Reference)
TOT	1.7 (1.3-2.3)	2.1 (1.5-2.9)
UIT	10.7 (8.9-12.8)	11.5 (9.3-14.3)
Colposuspension	1.3 (0.9-1.8)	1.4 (1.0-2.0)
Pubovaginal slings	1.1 (0.8-1.9)	1.2 (0.7-1.9)
Miscellaneous	2.2 (1.6-2.8)	2.1 (1.5-2.8)

CI Confidence interval

TVT Tension- free vaginal tape

TOT Transobturator tape

UIT Urethral injection therapy

[a] Adjusted for age, department volume, and calendar effect (1998-2002, 2003-2007).

4.2 Study II

From 1998 to 2007, 5820 women (mean age 55.4 ± 12.1 years) had a synthetic MUS for UI, and 354 (6 %) were reoperated within a five-year period (Table 3). Women from low, medium, and high volume departments underwent reoperation to the same extent.

At baseline, 467 synthetic MUSs (8%) were implanted at low volume, 1429 (24.6%) at medium volume, and 3,924 (67.4%) at high volume departments.

Table 3 Baseline characteristics for women with midurethral sling surgery, 1998-2007, Denmark

	Complete cohort	No reoperation	Reoperation	P value
N	5820	5466	354	
Age, years , Mean ± SD	55.4 (12.1)	55.3 (12.0)	56.6 (13.3)	0.06 [a]
Low volume Department (%)	467 (100)	445 (95.3)	22 (4.7)	0.23[b]
Medium volume Department (%)	1429 (100)	1343 (94.0)	86 (6.0)	
High volume Department (%)	3924 (100)	3678 (93.7)	246 (6.3)	

[a] Student´s t-test

[b] χ^2- test for trend

At low volume departments 122 TOTs out of 467 synthetic MUSs (26.1%) were implanted at baseline, which was significantly more than at medium and high volume departments where 149/1429 (10.4%) and 519/3924 (13.2%)(both $p < 0.001$) TOTs were implanted (Tables 4, 5).

Table 4 Baseline characteristics for women with TVT, 1998-2007, Denmark

	Complete cohort	No reoperation	Reoperation	P value
N	5030	4745 (94.3)	285 (5.7)	
Age, years, Mean ± SD	55.6 (12.1)	55.5 (12.0)	56.2 (13.1)	0.39 [a]
Low volume Department (%)	345 (100)	336 (97.4)	9 (2.6)	0.098 [b]
Medium volume Department (%)	1280 (100)	1203 (94.0)	77 (6.0)	
High volume Department (%)	3405 (100)	3206 (94.2)	199 (5.8)	

TVT Tension- free vaginal tape

[a] Student´s t-test

[b] χ^2- test for trend

Table 5 Baseline characteristics for women with TOT, 1998-2007, Denmark

	Complete cohort	No reoperation	Reoperation	P value
N	790	721	69	
Age, years, Mean ± SD	54.2 (12.4)	53.8 (12.1)	58.3 (14.2)	< 0.004 [a]
Low volume Department (%)	122 (100)	109 (89.3)	13 (10.7)	0.91 [b]
Medium volume Department (%)	149 (100)	140 (93.9%)	9 (5.1)	
High volume Department (%)	519 (100)	472 (90.9%)	47 (9.1)	

TOT Transobturator tape

[a] Student´s t-test

[b] χ^2-test for trend

Women having repeat surgery subsequent to a TOT were at baseline significantly older than women who did not have a reoperation (58.3 vs. 53.8 years, $p < 0.004$) whereas this difference was not found for TVT (56.2 vs. 55.5 years, $p = 0.4$).

In the first period (1998-2002), TVT was introduced and the first choice treatment at reoperation was a new TVT (45.7%)(Table 6).In the second period (2003-2007) both synthetic MUSs had come into use, and in this period a repeat synthetic MUS was still the first choice (45.5%).

It was more common that women with failure of a TVT had a TVT again (37.2%) rather than the TOT procedure (6.3%). For TOT, the reverse was observed, as a TOT was preferred (42.0%) over a TVT (10.4%). As a second choice, UIT was popular during both periods, 30.4% and 37.7%.

Table 6 Repeat procedures after failed midurethral slings, 1998-2007, Denmark

	Period 1998-2002						Period 2003-2007						
Baseline	TVT	UIT	Colpo-suspension	Pubo vaginal slings	Mis cellanous	Total	TVT	TOT	UIT	Colpo-suspension	Pubo vaginal slings	Mis cellanous	Total
TVT (%)	21 (45.7)	14 (30.4)	2 (4.4)	3 (6.5)	6 (13.0)	46 (100)	89 (37.2)	15 (6.3)	94 (39.3)	2 (0.84)	4 (1.7)	35 (14.6)	239 (100)
TOT (%)[a]	-	-	-	-	-	-	7 (10.4)	29 (42.0)	22 (31.9)	0 (0.0)	3 (4.4)	8 (11.6)	69 (100)
Total (%)	21 (45.7)	14 (30.4)	2 (4.4)	3 (6.5)	6 (13.0)	46 (100)	96 (31.2)	44 (14.3)	116(37.7)	2 (0.7)	7 (2.3)	43 (14.0)	308 (100)

TVT: Tension- free vaginal tape

TOT: Transobturator tape

UIT: Urethral injection therapy

[a] Blank cells: Transobturator tape was first implemented in 2003 in Denmark and therefore no data appear in these cells (1998-2002).

At reoperation, 289 women (82%) were treated at the same department where the primary synthetic MUS had been performed, 22 women (7.6. %) at low volume, 71 women (24.5%) at medium volume and 196 women (67.8%) at high volume departments.

The remaining 65 women (18%) had their initial surgery at high volume departments, 45 of these (69.2%) were reoperated at highly specialized departments.

At low volume departments, four different treatments were offered, whereas at medium and high volume departments six different treatments were used (Table 7).

At low volume departments, TOTs were used in 40.9% of the repeat surgeries, in contrast to medium and high volume departments, where 6.9% and 11.8% were TOTs (both $p < 0.001$).

Table 7 Repeat surgery and department volume, 1998-2007, Denmark

	TVT	TOT	UIT	Colposuspension	Pubovaginal slings	Miscellanous	Total
N	117	44	130	4	10	49	354
Low volume Department	7 (31.8)	9 (40.9)	5 (22.7)	-	-	1 (4.5)	22 (100)
Medium volume Department	38 (44.2)	6 (6.9)	34 (39.5)	2 (2.3)	1 (1.2)	5 (5.8)	86 (100)
High volume Department	72 (29.2)	29 (11.8)	91 (37.0)	2 (0.8)	9 (3.7)	43 (17.4)	246 (100)

TVT Tension- free vaginal tape
TOT Transobturator tape
UIT Urethral injection therapy

4.3 Study III

Baseline characteristics

Between January 1, 2007 and December 31, 2011 a total of 731 women with first-time UITs were consecutively registered in the DugaBase. Among these, 650 women (88.9%) had one, 79 (10.8%) had two, and 2 (0.3%) had three UITs. The mean age was 64, the mean BMI 26.7 and 56.5% had MUI and 31% had SUI (Table 8). Patient characteristics related to surgeon and department volume are reported separately (Appendix 5). The low volume surgeon treated women who had a significantly higher BMI and with a higher ASA Classification (3-5) compared to the high volume surgeon.

Table 8 Patient characteristics for women with urethral injection therapy, 2007-2011, Denmark

Variables	**All**[1]
Age, years, mean (SD)	64.0 (13.9)
BMI, mean (SD)	26.7 (5.3) [2]
Type of UI	
Stress	152/490 (31.0)
Urgency	35/490 (7.1)
Mixed	277/490 (56.5)
Not specified	26/490 (5.3)
Smoking	100/505 (19.8)
Alcohol units per week, mean (SD)	2.8 (4.4) [3]
ASA	
1-2	394/458 (86.0)
3-5	64/458 (14.0)
Parity, mean (SD)	2.3 (1.2)[4]
Previous surgery	
Hysterectomy	161/505 (31.8)
UI surgery	89/504 (17.7)
POP surgery	91/500 (18.2)
Use of preoperative medication	
Oestrogen	422/672 (62.8)
Antimuscarinic drugs	175/672 (26.0)
Diuretics	278/672 (41.3)
Other drugs	36/672 (5.4)

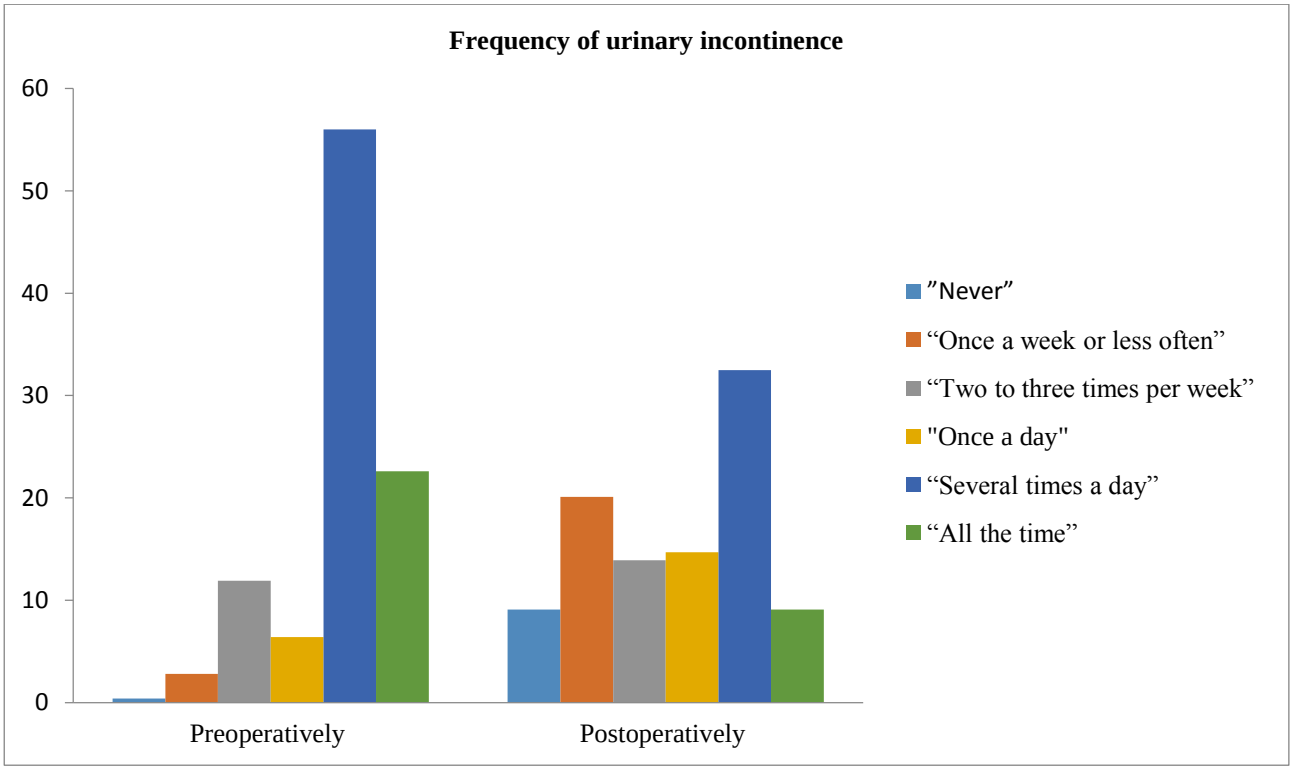
[a] Number/total of women (%), n = 731, unless otherwise stated.[b] N = 528[c] N = 420[d] N = 564.

BMI body mass index, ASA American Society of Anesthesiologist's Classification, UI Urinary incontinence, POP Pelvic organ prolapse, Other drugs desmopressin, imipramine or duloxetine.

Among the 252 women who pre- and postoperatively had answered both questionnaires, 75 (29.8%) had success and 23 (9.1%) achieved no leakage at all at three months follow-up (Fig.5).

The mean total ICIQ-SF score was 16.0 (SD 3.8) and after injection 10.6 (SD 6.2) ($p < 0.001$). There was a statistically significant improvement on all three scores of the ICIQ-SF (data not shown).

Figure 5 Frequency of urinary incontinence, before and after treatment
- **based on women who had completed questionnaires both pre- and postoperatively**



UIT was performed at 16 departments, of which four high volume departments performed 547 of 814 UITs (67.2%). There were more UITs performed by high volume surgeons at high volume departments, 368/472 (75.9 %) compared to low volume departments, 117/282 (24.1%), ($p < 0.001$) (data not shown).

Among the patient characteristics, the severity of UI preoperatively decreased the likelihood of cure significantly in all ICIQ-SFs scores (data not shown). Similarly women with a preoperative use of antimuscarinic drugs had a significantly lower chance of cure on the frequency score (adjusted OR 0.14; 95%, CI 0.04-0.41) and the amount score (adjusted OR 0.33; 95%, CI 0.13-0.82) (Table 9).

There was no influence of MUI or UUI on the chance of cure or on the rate of hospital contacts.

Women treated by a high volume surgeon had an increased chance of cure on the frequency score compared to women treated by a low volume surgeon (adjusted OR 4.51; 95% CI, 1.21-16.82), and a lower risk of hospital contacts (adjusted OR 0.35; 95% CI, 0.16-0.79).

The risk of hospital contacts was also lower for women treated at a high volume department (adjusted OR 0.27; 95% CI 0.09-0.76).

Table 9 Uni- and multivariate analyses of variables potentially involved in cure, ICIQ-SF (Frequency, Amount and Impact)

Variables	**Frequency**		**Amount**		**Impact**	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
	Odds ratio (95%, CI)	Odds ratio (95%, CI)	Odds ratio (95%, CI)	Odds ratio (95%, CI)	Odds ratio (95%, CI)	Odds ratio (95%, CI)
Age, years	0.98 (0.96-1.00)	0.99 (0.96-1.03)	0.98(0.96-1.00)	0.98 (0.95-1.01)	1.01 (0.98-1.03)	1.02 (0.98-1.05)
BMI, kg/m^2	**0.93 (0.87-0.99)**	0.94 (0.86-1.01)	0.99 (0.93-1.04)	1.01 (0.93-1.08)	0.98 (0.92-1.03)	1.00 (0.94-1.08)
Type of UI						
Stress	Reference	-	Reference	-	Reference	-
Urgency	0.42 (0.12-1.46)		0.65 (0.22-1.93)		1.15 (0.37-3.55)	
Mixed	1.19 (0.63-2.24)		0.96 (0.52-1.78)		1.76 (0.88-3.48)	
Not specified	2.82 (0.70-11.22)		0.55 (0.14-2.12)		0.77 (0.19-3.12)	
ASA						
1-2	Reference	Reference	Reference	Reference	Reference	Reference
3-5	**0.53 (0.33-0.84)**	0.67 (0.34-1.3)	0.67 (0.43-1.05)	0.81 (0.43-1.51)	0.80 (0.50-1.28)	0.80 (0.42-1.51)
Parity	**1.31 (1.03-1.66)**	1.26 (0.97-1.65)	**1.34 (1.07-1.69)**	1.09 (0.84-1.4)	1.11 (0.87-1.42)	1.13 (0.87-1.47)-
Previous surgery						
Hysterectomy	1.18 (0.65-2.12)	1.12 (0.46-2.69)	1.72 (0.92-3.21)	1.44 (0.59-3.48)	1.09 (0.57-2.07)	0.64 (0.27-1.54)
UI surgery	1.21 (0.59-2.46)	1.82 (0.56-5.93)	0.99 (0.45-2.14)	0.62 (0.18-2.09)	0.68 (0.30-1.51)	1.18 (0.37-3.74)
POP surgery	1.07 (0.51-2.26)	0.39 (0.10-1.54)	1.47 (0.65-3.34)	5.62 (1.25-25.32)	0.84 (0.34-2.04)	0.80 (0.21-2.96)
Preoperative medication						
Oestrogen	0.62 (0.34-1.14)	0.62 (0.25-1.57)	0.55 (0.29-1.00)	0.56 (0.22-1.40)	0.78 (0.41-1.49)	1.12 (0.46-2.7)
Antimuscarinic drugs	**0.34 (0.16-0.71)**	**0.14 (0.04-0.41)**	**0.42 (0.21-0.83)**	**0.33 (0.13-0.82)**	0.92 (0.45-1.86)	0.87 (0.35-2.14)
Diuretics	0.81 (0.45-1.46)	0.99 (0.4-2.43)	1.29 (0.72-2.3)	0.75 (0.32-1.78)	1.24 (0.67-2.31)	0.88 (0.37-2.10)
Surgeon volume						
Low	Reference	Reference	Reference	Reference	Reference	Reference
Medium	2.25 (0.86-5.88)	1.95 (0.57-6.58)	0.44 (0.17-1.1)	0.39 (0.15-1.04)	1.3 (0.49-3.46)	1.03 (0.3-3.58)
High	**2.59 (1.11-5.99)**	**4.51 (1.21-16.82)**	0.86 (0.39-1.9)	0.64 (0.17-2.25)	1.42 (0.61-3.33)	1.83 (0.48-6.94)
Department volume						
Low	Reference	Reference	Reference	Reference	Reference	Reference
High	0.84 (0.47-1.50)	0.96 (0.26-3.58)	1.01 (0.57-1.78)	1.5 (0.42-5.29)	0.82 (0.44-1.50)	0.72 (0.19-2.7)

ICIQ-SF The International Consultation on Incontinence Questionnaire Short Form.
CI Confidence interval, BMI body mass index, ASA American Society of Anesthesiologist's Classification, UI Urinary incontinence, POP Pelvic organ prolapse, Other drugs desmopressin, imipramine or duloxetine.
Cure was dichotomized (See Appendix1) and throughout all analyses, adjusted by the preoperative ICIQ-SF- score ("severity").
Adjustment was made for age (continuous), BMI(continuous), ASA Classification (reference 1-2 (reference), yes), parity (continuous) previous hysterectomy (no (reference), yes), previous UI surgery (no (reference), yes), previous POP surgery (no (reference), yes), use of oestrogen preoperatively (no (reference), yes), use of antimuscarinic drugs (no (reference), yes) preoperatively, and use of diuretics preoperatively (no (reference), yes).

At baseline sensitivity analysis showed only a few differences in patient characteristics, department and surgeon volume between women who answered both ICIQ-SF total pre- and postoperatively and women who did not; for BMI (26.4 *vs.* 28.1, p = 0.02), for ASA (ASA 1-2 86.9% *vs.* 74.5%; ASA 3-5 13% *vs.* 25.5%, p = 0.03) for department volume (low 34.5% *vs*. 46.1; high 65.5% *vs.* 53.9%, p = 0.02) and surgeon volume (low 18.2% *vs.* 12.4%, medium 23.8% *vs.* 15.7%; high 58.6% *vs.* 71.9%, p=0.03). Women who had completed both questionnaires had less UI (16.5% *vs*. 32.2%, p = 0.03) and POP surgery (15.6 *vs.* 32.3%, p = 0.02) than women who had only completed the questionnaire postoperatively. There were no differences in patient characteristics between women who had completed both questionnaires and women who had only completed the questionnaire preoperatively (data not shown).

There were no differences in severity of UI pre or postoperatively with respect to completion of the questionnaires.

5. General discussion

5.1 Reoperation for urinary incontinence

To the best of our knowledge, no studies based on an entire nation have reported on the rate of reoperation after TVT. We found a cumulative rate of 6% after TVT within a five-year period (Study I). An Austrian single centre study (n=101) showed a similar rate of reoperation after TVT of 6% after five years (14) whereas two other studies based on one (n=141) and two centres (n= 483) at ten years of follow-up showed an incidence of 7.8% and 2.8%, respectively (48, 49). Three major population-based cohort studies have evaluated rates of reoperation after all sling types and showed comparable rates of reoperation at five years follow-up (5% and 8%)(all sling types) (12, 46) and 3.76% at seven years follow- up (synthetic MUSs) (46).

It is difficult internationally to establish the study population, the surgeons and their criteria for choosing surgical intervention, and the patient's willingness to undergo reoperation influence a standard for acceptable rates of reoperations for synthetic MUSs, as the risk of reoperation. The study population of Taiwan, for example, is likely to differ from the population in Europe or the USA and thereby its prevalence of UI and the need for surgical treatment. A high rate of surgical intervention does therefore not necessarily mean that it is used inappropriately since it might also reflect that the need for surgery is higher in a given region (79-81).

As UI is not a life-threatening disorder, there will never be an absolute indication for surgery and across 15 countries it has been demonstrated that there is large regional variation in surgical intervention for UI (45). It is reasonable to assume that areas with a high rate of surgical intervention for UI will similarly have a high rate of reoperations. However, these aspects are not well-explored (82).

Financial incentives such as reimbursement can also influence the incidence of surgery for both patients and healthcare providers (80). Because Denmark, unlike the USA and Taiwan for example (12, 68, 83), offers free access to specialist healthcare, financial constraints are less likely to be limiting factors for reoperation.

At the national level, it is also difficult to set a standard for an acceptable rate of reoperation after synthetic MUSs. Superficially, the rate of reoperation after synthetic MUSs appears to be a viable quality indicator as it reflects the failure of a primary procedure (84, 85) and is easy and

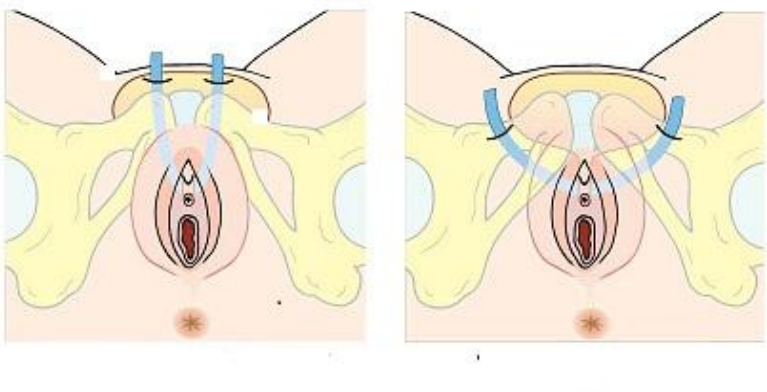
inexpensive to identify (86). There are however disadvantages to using it comparatively across hospital departments (86, 87). Firstly, the rate represents not only the failure of a primary procedure, but it also represents women with a new onset of UI after surgical treatment (84, 85). Secondly, the risk of confounding is higher if information is based exclusively on administrative data or clinical data not adjusted for patient-related factors (80). Thirdly, as the number of reoperations after synthetic MUS is generally low (50, 88) and even lower at the respective departments (89), this will impede the statistical precision (21, 89). Thus, the rate of reoperation for synthetic MUS is less valid when comparing departments, but the relative quality at each department can, to some degree, be assessed over time.

The observation that TOT was associated with a significantly higher risk of reoperation is new in the literature since previous meta-analysis (15-17) and a Cochrane-study (2009) (18) based on short and mid-term follow-up studies concluded that there was no statistically significant difference in the risk of reoperation between TVT and TOT (RR, 1.52; 95% CI 0.90 to 2.59). This study was based on five randomized controlled trials (RCTs) and included only 746 women and the follow-up period did not extend beyond 12 months (11, 90-93). In contrast, our study included 5820 women and a follow-up period of five years. Previous studies with longer follow-ups (3 to 6.5 years) (11, 94, 95) and the recently updated Cochrane (2015) (published after Study I) supplemented by longer follow-up periods also support the contention of our observations (96). Thus, in the Cochrane short-term follow-up ($\leq$ 1 year) based on 1402 women the risk is similar for both synthetic MUSs (RR, 1.64; 95% CI 0.85 to 3.16). However, in the mid-term follow-up (1 to 5 years) (n= 355) (RR, 21.89; 95% CI 4.36- 109.77) and in the long-term follow-up $\geq$ 5 years) (n = 695) (RR, 8.79; 95% CI 3.36-23.00), the risk of reoperation was higher for TOT than for TVT (Appendix 6) (96).
From a clinical perspective, it seems logical, for more reasons, that the risk of reoperation is higher for TOT. There are other objective outcome measures, which also show a lower effectiveness and durability of TOT compared to TVT.
An RCT of 404 women with a five-year follow-up has thus documented that *treatment success* measured as "no retreatment for SUI" (behavioural, pharmacological, pessary or surgical) and "no self-reported SUI" was significantly lower for women with TOT compared to women with TVT (43.4% *vs.* 51.3%, 95% CI-1.4, 17.2) (97).

A low *maximum urethral closure pressure* (MUP) is associated to severe UI (11, 98-100) and the MUP has proved to decrease significantly with increasing age, after the woman has passed the age of 25 years (101). Therefore, it also seems reasonable that women with a low MUP are documented to have significantly less success with TOT than with TVT (11, 98-100).

Anatomically there are differences between TVT and TOT in compression of the urethra, which might explain the differences in effectiveness and durability (100).
Both slings rely on the hammock hypothesis and the integral theory (102-104), where continence is achieved, by placing a vaginal tape underneath the mid-urethra. The TVT thus reinforces the weakened pubovaginal ligaments without tension (104). The most common complications with TVT (*i.e.* bladder perforation and blood vessel injury) have been associated with the passage of the trocars through the retropubic space (99). The TOT may be safer because the trocars pass through the medial obturator membrane avoiding the retropubic space.
As the TOT course is more horizontally under the urethra than the TVT, this leads to less lateral wall support and thereby the risk of obstruction of the urethra is reduced (99).

Figure 6
TVT procedure in which the synthetic tape enters and exits via the retropubic space (left).
TVT-O procedure in which the synthetic tape enters and exits via the obturator membrane (right).



5.2 Repeat surgery after failed midurethral slings

There is currently little knowledge based on national populations on which procedure is used after a failure of synthetic MUSs and it is therefore difficult to assess and discuss which procedures should be used (50). In this nationwide population-based study of 5820 women a synthetic MUS was the first choice (Study II), which probably reflects the fact that the synthetic MUS was also the gold standard for primary surgery.

The synthetic MUSs were used in 45% of women in both periods (1998-2002) and (2003-2007), whereas two other population-based cohort studies reported a more frequent use of synthetic MUSs (52, 83).

UIT was a frequent choice for repeat surgery, which is natural as the main indication is the second-line treatment in women not suitable for major surgery (11). It was however more frequently used (42%), compared with the UK (14%) and Taiwan (11%) (52, 83) indicating that the approach in Denmark is more conservative compared with that in the UK and Taiwan.

Finally, Burch colposuspension and pubovaginal slings were seldom chosen for reoperation, as was also observed in the UK (52) and this probably reflects the fact that both procedures are rarely used as primary surgery for UI (52). In Taiwan, Burch colposuspension and pubovaginal slings were frequently chosen for repeat surgery after a failed synthetic MUS and this is probably also due to the higher rate of use as primary UI surgery in Taiwan (83).

5.3 Urethral injection therapy for female stress and mixed urinary incontinence

This national population-based cohort study of transurethral application of PAGH among 731 women from 2007 through 2011 is the first study which is representative of a clinical setting (Study III). To date current knowledge of UIT with PAGH has been based on ten studies with a follow-up period of one to three years (23, 59-67), of which four were large-scale studies (n= 135-256) (23, 62, 65, 66) and the remaining small-scale studies (n = 20-82) (59-61, 63, 64, 67) (Table 8).

The short follow-up period differed from the other studies on PAGH. Moreover, the majority of the studies reported results representing both one and more UITs (23, 59-61, 63, 64, 66). The efficacy of PAGH is highest at three months (23, 62, 65, 66) after which the majority of women need repeat surgery (19, 20). It is in this perspective that results representative of women with first-time UIT should be evaluated.

Overall, the efficacy of PAGH in the present study might seem in the lower end of the spectrum in comparison to the literature (23, 60-67). Prospective studies, of which two were large multicentre studies (23, 62) had extremely strict inclusion criteria. For example, none of the studies included

women with prior surgical treatment for UI (23, 61, 62, 65) and one study excluded women with MUI (61). We cannot rule out that there is a tendency to positive selection since the largest studies of PAGH to date were funded by the industry (23, 62, 65). Studies based exclusively on women with severe UI or previous surgical treatment for UI reported equivalent (65) or slightly better results compared to ours (60, 66, 67).Women in previous studies might have benefitted from more repeat injections. However, only one study reported cure after the second injection and the rate was lower than for the first UIT (62).

Table 10 Studies on urethral injection therapy with polyacrylamide hydrogel

First author , date	Type of study	Size	Follow-up	Age	Subjective outcome	ICIQ-SF total Preoperatively	ICIQ-SF total Postoperatively	P-value	Exclusion-criteria	Funding
Lose, 2010 (23)	Prospective multicentre Observational	135	12 months	56 (29-82)	ICIQ-SF VAS	15	7	< 0.001	Previous UI surgery, UIT, Medication for UI	Industry
Trutnovsky, 2011 (63)	Prospective Observational	54	9 months	69 (41-87)	IOQ	-	-	-	-	None
Toozs-Hobson, 2012 (62)	Prospective multicentre Observational	135	24 months	-	ICIQ-SF VAS	15	7	< 0.001	Previous UI surgery, UIT, Medication for UI	Industry
Maggiore, 2013 (61)	Prospective Observational	82	12 months	54.3 (±7.9)	ICIQ-SF PGI-I IIQ-7	14.2	4.4	< 0.001	Previous UI surgery, POP surgery, OAB, MUI, POP >2	Industry
Beraru, 2014 (60)	Prospective Observational	80	18.6 months	72.8 (±13)	ICIQ-SF PGI-I	17	13	$< 10^{-4}$	-	None
Martan, 2014 (59)	Retrospective observational	52	22 months	70 (18-90)	ICIQ-SF VAS	17.6	10.6	< 0.001	-	None
Sokol, 2014 (65)	Single blind Randomized Controlled Trial	229 *vs.* 116	12 months	58.5 (23.3-93.4) 56.7	ICIQ I-QOL And PISQ	-	-	-	-	Industry

				(29.5-85.4)						
2014, Vecchioli-Scaldazza (64)	Prospective observational	20	24 months	84.5 (80-87**)**	QOL IIQ-7 PGI-I VAS	-	-	-	-	None
2015 Pai (66)	Prospective	256	38 months	58.8 (31-93)		15	7	< 0.001		None
2016, Zivanovic (67)	Prospective observational	60	12 months	71.7 (10.7)	VAS	-	-	-	MUI, tape location Severely outside the midurethral zone, Obstructive tape location or post void residual (volume >100ml.	None
Hansen MF (Manuscript)	Retrospective Observational	731	3 months	64.0 (±13.9)	ICIQ-SF	16	10.6	P < 0.001	-	None

ICIQ-SF International Consultation on Incontinence Questionnaire –Short Form

IOQ Incontinence Outcome Questionnaire

MUI Mixed UI

OAB Overactive bladder syndrome

PGI-I-score Patient´s Global Impression of Improvement

POP Pelvic Organ Prolapse

UI Urinary incontinence

5.4 Department volume, surgeon volume and patient-related factors

Department volume had no influence on the risk of reoperation following all types of surgical treatment for UI (Study I). The risk of reoperation was also not likely to be affected by the learning curve, as the cumulative incidence of reoperation after synthetic MUSs remained stable over the study period (1998-2007) as it did for TVT and TOT. This is in accordance with a previous observation, which also found no influence of the learning curve on the risk of reoperation after sling surgery (12). Whether or not the department volume influences the risk of reoperation after synthetic MUSs remains controversial as one population-based cohort study found no difference (46) and two other population-based cohort studies found an increased risk of reoperation after TVT and synthetic MUSs at low volume departments (83, 105). This most likely also depends on, how department volume is defined in the studies.

We could only indirectly evaluate the influence of department volume on repeat surgery after failure of a synthetic MUS (Study II) due to its descriptive study design, which did not include results following the second procedure. The majority of women had repeat surgery at the same department where they had undergone a primary MUS (82%) procedure even though the DHMA and the Danish Society of Obstetrics and Gynaecology (DSOG) recommend that complicated cases should be referred to a highly specialized department (36, 106).

A number of factors indicated that repeat surgery after failed synthetic MUSs was best undertaken at highly specialized departments. More treatment modalities were in use at high volume departments than at low volume departments. This finding was reinforced by the fact that there were also fewer surgical treatments offered at baseline at low volume departments (Study I). Pubovaginal slings were not used as repeat surgery and similarly not a part of the standard assortment at baseline. UIT was selected for repeat surgery but rarely at baseline, which meant that low volume departments were less practised in this procedure. Last but not least, there were significantly more TOTs implanted at low volume departments as repeat surgery and at baseline. A repeat TOT is associated with poorer outcome (98, 107-109) and as a practice not evidence-based.

We evaluated the influence of all three parameters: Department volume, surgeon volume and patient-related factors in respect of UIT (Study III). The influence of department was not immediately as apparent as the influence of surgeon volume. Because department volume represents a complex of organizational factors while surgeon volume reflects individual skills (21,

22), logically, the influence of surgeon volume should be more demonstrable. A previous multicentre study similarly showed borderline significant better results on the ICIQ-SF for departments, which injected ≥15 UITs *per* year. This study was not adjusted for patient-related factors (23). The explanation for the better outcomes obtained at high volume departments is in our study more likely explained by the positive correlation between high volume departments and high volume surgeons.

The high volume surgeon (>75 UITs) had significantly better outcomes on the frequency score of the ICIQ-SF and a significantly lower risk of contacts to hospital within 30 days. The influence of the surgeon volume was, however, only present in one of three items of ICIQ-SF. However, as *e.g.* the impact score was not susceptible to any risk factors it was also not likely, that it would be influenced by surgeon volume. Until now, only two studies have assessed that there seems to be a learning curve (23, 110).
The learning curve for UIT would appear to be high (>75 UITs) compared to TVT which has a learning curve of 20 procedures (29-32). One possible explanation is that UIT is a technically complicated procedure (23) and in Denmark not routinely performed.

Finally, an interesting observation was that women treated by the low volume surgeon had a significantly higher BMI and a higher ASA score (3-5) than women treated by the high volume surgeon. Similar observations have been made within other surgical specialties; that the low volume surgeon treated patients who were older and had higher preoperative risk factors (22, 111). This practice does not seem appropriate neither for patients nor for surgeons.

Among patient-related factors, only a few were associated with a lower cure. The severity of UI preoperatively was consistently and independently associated with a lower cure based on all ICIQ-SF scores. The use of antimuscarinic drugs preoperatively decreased the likelihood of cure.

MUI and UUI were not patently predictors of lowering the cure. However, women who redeem prescriptions of antimuscarinic drugs often have either MUI or UUI. This might therefore indicate that women with the most severe MUI and UUI have less chance of cure. Previous studies only found borderline poorer outcome for women with MUI injected with PAGH (23, 62, 64).

The right patient for UIT is still being disputed and predictors of lower success among women are not well understood (58, 112). It seems paradoxical that the predictors of poorer outcome were found among women who most often have UIT, *i.e.* women with severe UI, MUI and UUI who are not suitable for a synthetic MUS. This emphasizes the need for proper patient counselling in order to provide women with realistic expectations regarding the outcome.

In short, in all three studies there was either a positive or a neutral association between department volume and outcome, which is in accordance with the literature as a negative association between the two has never been fully demonstrated (22). It was indicated, that better outcomes could be achieved if repeat surgery after failed synthetic MUSs and UIT was restricted to fewer hands. It seems logical and rational that medical disorders that are rare or procedures, which are rarely performed, should not be performed at all departments but at highly specialized departments; this being the very purpose of such departments.

6. Methodological considerations

Interpretation of the results described in this thesis and the implications for clinical work should be done with caution taking certain methodological strengths and weaknesses into consideration, as described below**.**

The main strengths of the thesis were that the studies were national-wide population-based cohort studies, had a long-term follow-up (studies I, II) and a large sample size.

6.1 Nationwide population-based cohort studies

The three studies were based on registries of national populations. A nationwide population-based approach in Denmark is both logical and feasible as the Danish National Patient Registry is internationally considered the most comprehensive of its kind and the availability of a national health administrative registry, combined with a personal identification number, is almost unique to Denmark (68-70) . This combination is a major strength as it permitted a study of follow-up after primary surgery for UI not only at a single hospital department, but at all departments nationwide in Denmark.

It is mandatory by law for all hospital departments and private hospitals to report to the Danish National Patient Registry. Furthermore, there is no reimbursement for departments, which do not report to the registry. Studies of procedure codes have thus shown high validity (71).

Access to data from a national clinical database (The DugaBase) and the Danish Register of Medicinal Products Statistics permitted us to explore aspects of UIT, which have scarcely been studied (in terms of surgeon volume for example) and to report on several patient-related factors.

It is mandatory to report to the DugaBase and the database completeness is high today. For eleven main variables the validity has shown be high (90-100%) when comparing information from the database with the medical records (42).

6.2 Long-term follow-up

The follow-up at five years strengthened our observation of differences in risk of reoperation after TVT and TOT, as the current knowledge of risk of reoperation after synthetic MUS derived mainly from studies based on shorter follow-up.

6.3 Sample size

The large population was a strength as it increased the likelihood of detecting a true difference in the risk of reoperation between TVT and TOT (Study I). Although the sample size was reduced with respect to outcome (Study III) and in logistic regression when adjusting for several variables, the study is still the second largest study on PAGH (Table 10). The relatively large sample size supported our observation of a learning curve within UIT and that the severity of UI preoperatively and the use of antimuscarinic drugs are associated with lower cure. This gave further credence to the observation that there was no influence of several other variables. A smaller sample would be more likely to produce non-significant results, even if a true difference existed (Type 2 error).

The main limitations were the possibility of selection bias, confounding, information bias, and shortness of follow-up.

6.4 Selection bias

A selection bias is a systematic error in a study that stems from the methods used to select the study population and from factors that have influence on it (113). It arises when the association between exposure and outcome differ for those who participate and those who do not participate in the study. The studies based on the Danish National Patient Registry included nearly all procedures for UI performed at all hospital departments in Denmark, which reduces the risk of selection bias (Studies I, II).

The database completeness of the DugaBase was low at the beginning of our study period and we were therefore not able to exclude some selection bias, as not all departments reported to the database (Study III). Of 1346 procedures in the Danish National Patient Registry, 814 were registered in the DugaBase. Of these, 16 out of 22 departments were registered in the DugaBase. The remaining six departments not registered in the DugaBase contributed with only 61 of the 1346 (4.5%) procedures. All four high volume departments were registered both in the DugaBase and the Danish National Patient Registry and contributed with 547/814 (67.2%) and 874/1346 (64.7%).

The data completeness has constantly been low since the establishment of the DugaBase due to the fact that there is in Denmark a heterogeneous way of follow-up. Some departments perform follow-ups routinely, whereas other departments only follow-up on complicated patients. This poses a selection bias, which is important to take into consideration when evaluating outcome and the influence of department volume. Sensitivity analysis showed only minor differences in patient

characteristics at baseline and no differences in severity of UI pre or postoperatively with respect to completion of the questionnaires. This indicates that there is no difference in outcome between the included and non-included women.

6.5 Confounding

A confounding variable is a variable associated with both exposure and outcome (113). To minimize a false positive estimate of association (Type 1 error), researchers must attempt to control for confounders. We had no access to clinical data (except for the patient's age) or information on the surgeon volume (Studies I, II).

There is some evidence that, in certain subgroups of women, outcomes after TVT and TOT are different (100).Women with MUI seems to benefit from receiving a TOT (99, 114) whereas women with severe UI (*i.e.* sphincter deficiency) have more success with TVT (11, 98, 100). This could result in confounding by indication. However, the significance of confounding by indication seems to be minor. In practice, the indication for which the sling type should be implanted is not based on patient characteristics. Unpublished results have shown that 98% of Danish hospital departments (2010-2011) selectively use either TVT or TOT (115) . The remaining departments used both equally.

The lacking information on surgeon volume could also be a confounding variable (Studies I, II). It is possible that the difference in the risk of reoperation between TVT and TOT could be explained by different levels of surgeon volume. There was, however, no initial learning curve for TVT or TOT as the risk of reoperation remained stable across all years.

We concluded that repeat surgery after failed MUSs was better undertaken at high volume departments (Study II), but we could only indicate this, as we had no information on surgeon volume or clinical data.

In Study III, we evaluated the influence of department and surgeon volume. The low-volume surgeon treated women with a significantly higher BMI and a higher ASA score (3-5) compared to medium- and high-volume surgeons. We adjusted for these and several other patient-related factors thus reducing the risk of confounding.

6.6 Information bias

Information bias can arise in a study as a systematic error if data is collected erroneously, and if this results in a variable being placed in an incorrect category it is called misclassification (113) . The issue of misclassification is relevant to address for Studies I and III as the variables of exposure (department volume) and outcome (reoperation) are poorly defined within the field of urogynaecology.

The definition of department volume is specific for the procedures used within a given specialty and is therefore not generalizable across specialties (22). As only a few studies have explored aspects of department volume within the surgical treatment for UI (23-26, 46, 82, 83) there is no global definition of department volume. Previous studies defined high and low volume departments using the median of annual surgical procedures for UI (46, 82). Similarly, we defined department volume based on the annual surgical procedures for UI by calculating tertiles from these (high, medium, low volume) (Studies I, II). There are, however, limitations to this definition. Comparisons of department volume studies will not be directly comparable internationally, as the absolute number of annual surgical procedures for UI will differ across countries (45).

For UIT it was not meaningful to define department volume based on the median of annual procedures of UI (Study III). As a relatively small number of UITs has been performed in Denmark over the last decade, the number of UITs rather than the number of all procedures for UI characterized the ability to perform the procedure. The same definition of high (≥15 UITs *per* year) and low (<15 UITs *per* year) volume departments was used as previously (23).

In surgical literature a reoperation is defined as definite (include all procedure codes) or indefinite (only certain procedure codes) and combined with a diagnosis code (116), as applicable. The time frame specified from primary procedure to reoperation will, if short (*i.e.* one week); often reflect reoperations due to surgical complications, whereas a longer time frame indicates whether the primary procedure was successful.

We defined a reoperation as definite using all NOMESCO-procedure codes for UI except for removal/excision of sling (as not registered in the Danish National Patient Register) and a follow-up of five years. Previous population-based cohort studies used similar definitions with follow-up from seven to nine years (12, 83) except for one study, which excluded UIT at baseline and at reoperation (46).

The definition of reoperation might for synthetic MUSs (Studies I, II) cause underreporting, to some extent through misclassification as 'exclusive removal/excision of sling'. This will however be a non-differential misclassification with regard to both TVT and TOT and is hence of lesser significance.

6.7 Shortness of follow-up

The shortness of the follow-up period was a limitation of Study III, as it is difficult to evaluate the efficacy of UIT based on women who had received only a first injection. The efficacy of UIT is highest from one to three months, and it has been documented that the majority of women need two to three injections to achieve a satisfactory result. Routine, planned follow-up in Denmark for surgical treatment for UI is normally at three months, which is registered in the DugaBase. It was therefore not possible to include a longer follow-up for outcomes based on PROMs.

6.8 Generalizability

Generalizability beyond the studies is only relevant to address if there are no problems of internal validity (selection bias, confounding, and information bias). In the above section, these aspects have been addressed.

In Study I, we described the cumulative incidence of reoperations after different types of surgical treatment for UI and in Study II; we evaluated the choice of subsequent treatment after failed synthetic MUSs.

While we believe that the internal validity of both studies is high, it is difficult for outcomes regarding incidence and prevalence to be applied generally beyond the present studies as they are influenced by the study population the surgeons and their criteria for choosing surgical intervention. Similarly, the choice of subsequent treatment after failed synthetic MUSs might be influenced by access to medical care, and financial considerations for both the women and the health care providers.

With regard to association-outcomes, it is more relevant to address generalizability, since the causal relationship should not be population-dependent provided that the association is not substantially influenced by factors acting differently in different settings, which is unlikely in our case.

Sir Austin Bradford Hill proposed in 1965 a list of considerations to distinguish causal from non-causal associations (Fig.7) emphasizing the importance of many other factors than statistical significance testing (117).

We evaluated various exposures and we believe patient-related factors (*e.g.* age, severity of UI, use of antimuscarinic drugs) are to some extent generalizable, while we think organizational factors are difficult to extrapolate to different settings, as there are various definitions of department volume and surgical training differ among the countries.

Figure 7: "Causal criteria of Hill"

7. Conclusion

These studies contribute with new evidence on the following subjects according to the aims of the thesis:

7.1 Study I

This study provided physicians with a representative evaluation of the rate of reoperation after different surgical procedures for UI within a five-year period. The study is the first nationwide study, which evaluates the risk of reoperation after TVT and similarly the first comparative study on the risk of reoperation after TVT and TOT. There was influence of department volume on the risk of reoperation.

7.2 Study II

In this nationwide study of surgical treatment after failed MUSs a repeat MUS was the first choice treatment and a frequent second choice. There were fewer treatment modalities in the use at low volume departments in comparison to medium and high volume departments. Repeat surgeries after failed synthetic MUSs was in Denmark carried out at a decentralized level as the majority of women had repeat synthetic MUSs at the same department, which performed the primary surgery.

7.3 Study III

This national population-based cohort study demonstrated results which might seem lower than reported in the literature, but they were more representative of women of a daily clinical setting. Among patient characteristics there were only a few that were associated to lower cure. The severity of UI preoperatively was a strong predictor for lower cure and similarly a use of antimuscarinic drug preoperatively indicating a poorer outcome for women with severe MUI and UUI.

A learning curve for UIT was indicated and that the treatment should be restricted to fewer hands to improve the surgical education and consequently cure for women with UIT.

8. Future perspectives

8.1 The value of nationwide cohort studies

The registries and clinical databases representing national populations provide a substantial resource within the field of urogynaecology, since they allow us to obtain a large sample size over several years. The data are readily accessible (no informed consent required from the patient, no delaying investigations, and access to data at any time). The results are representative of daily clinical practice and surgeons with different experience. Last but not least, the clinical databases were initiated not-for-profit by national working groups of urogynaecologists.

On the contrary, the RCTs include smaller sample sizes and long-term follow-up is often very costly. Even if follow-up is performed, the clinicians are not always willing to wait or the slings have been removed from the market by the time the study is published. Furthermore, patients are 'selected' and the investigators conducting the studies are often experienced surgeons.

On the other hand, studies based on registries and clinical databases have their limitations. The quality of output, both for quality assessment and research, will of course depend on the quality of input. The risk of selection bias (missing data), confounding, information bias and many others will always be present and it is important that researchers take this into account. As registries and clinical databases primarily serve clinical purposes, information is not always as detailed as warranted or there is a shortness of follow-up.

8.2 The Danish National Patient Registry and the DugaBase

The Danish National Patient Registry and the DugaBase have proved to be valuable tools in research, as both today have high database completeness within the field of urogynaecology.

The database completeness was lower previously for the DugaBase, which hampered studies on the risk of reoperation with long-term follow-up. It would seem relevant in the future to conduct studies on the risk of reoperation and repeat surgery after synthetic MUSs based on the DugaBase in order to study the influence of patient-related factors and surgeon volume.

The risk of reoperation is "the tip of the iceberg" in demonstrating efficacy of a given procedure and as the completeness of data on other objective outcome measures (*e.g.* surgical complications) improves in the DugaBase, this should be included in future studies of TVT and TOT.

As Denmark is a small country, the number of repeat surgeries after failed synthetic MUSs is consequently small. It might therefore be relevant to collaborate internationally to provide more evidence for the best treatment after failed synthetic MUSs.

Women with severe UI and women who were treated with antimuscarinic drugs (severe MUI and UUI) preoperatively benefitted less from UIT and it is relevant in future studies to continue working on algorithms of which women stand to benefit most from UIT, and investigating more aspects of the learning curve, *e.g.* the threshold for acquiring the skill and which areas should be practiced.

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10. Appendices

10.1 Clinical indicators

The clinical indicators for urinary incontinence used for annually reporting in the DugaBase (2016)

Indicator Domain	Indicator	Type	Standard	Calculation (numerator/ denominator)
Waiting time 30 days (Indicator 1)	Time from receipt of referral at hospital to the first contact with a specialist	Process	Minimum 90%	Number of patients with ≤30 days between referral and first visit at hospital /Total number of patients with a surgery date.
Subjective Patient assessment of success (Indicator 3)	Subjective patient assessment of success after surgical treatment for UI	Result	Minimum 70%	Number of patients with the answer "Never" or "About once a week or less often" to "How often do you leak urine?" / Number of patients with surgical treatment for UI and an answer to the question.
Obstruction after surgical treatment for UI (Indicator 4) *(Removed from the DugaBase 2012)*	Degree of obstruction after surgical treatment for UI assessed by the amount of residual urine. It should be < 50ml.	Result	Minimum 90%	Number of patients with < 50 ml residual urine at follow-up visit/ Number of patients with surgical treatment and a measure of the residual urine at follow-up visit.
Need for further treatment (Indicator 9)	Need for further treatment after surgical treatment for UI	Result	Maximum 10%	Number of patients with a small or large need for further treatment at follow-up visit/ Number of patients with surgical treatment for UI and a need for further treatment.
A MUS	A MUS procedure due to	Result	Maximum	Number of patients

procedure due to recurrence or persistence of UI within two years of follow-up (Indicator 11) (*Introduced to the DugaBase 2012)*	recurrence or persistence of UI within two years of follow-up		5%	Who within two years follow-up have a synthetic MUS/ Number of patients with synthetic MUS at baseline
A MUS procedure due to recurrence or persistence of UI within five years of follow-up (Indicator 12) (*Introduced to the DugaBase 2012)*	A MUS procedure due to recurrence or persistence of UI within five years of follow-up	Result	Maximum 10%	Number of patients Who within five years follow-up have a synthetic MUS/ Number of patients with synthetic MUS at baseline
Assessment of UI after surgical treatment for UI (PGI-I-score) *(Introduced to the DugaBase 2014)*	UI after surgical treatment for UI assessed by the PGI-I-score	Result	Maximum ≥90 %	Number of patients with the answer "quite a lot better" or "much better" or "a little better" to "How will you describe your condition now, compared with the condition before surgery?" / Number of patients with surgical treatment for UI and an answer to the question.

MUS: Midurethral sling
PGI-I-score: Patient´s Global Impression of Improvement
UI: Urinary incontinence

10.2 Surgical procedures according to the Danish Nordic Medico-Statistical Committee (NOMESCO)

KDG00= Retropubic suspension of urethra

KDG01= Percutaneous endoscopic retropubic suspension of urethra

KDG10= Abdominovaginal suspension of bladder neck

KDG30= Suprapubic sling urethrocystopexy

KDG31= Percutaneous endoscopic suprapubic sling

KDG40= Suprabubic urethrocystopexy

KDG50= Transabdominal plastic repair of pelvic floor for UI

KDG96= Other operation on urethra or bladder neck for incontinence

KDG97= Other percutaneous endoscopic operation on urethra or bladder neck for incontinence

KDV20= Submucosal urethral injection

KDV22= Transluminal endoscopic submucosal urethral injection

KLEG00= Vaginal urethrocystorrhaphy

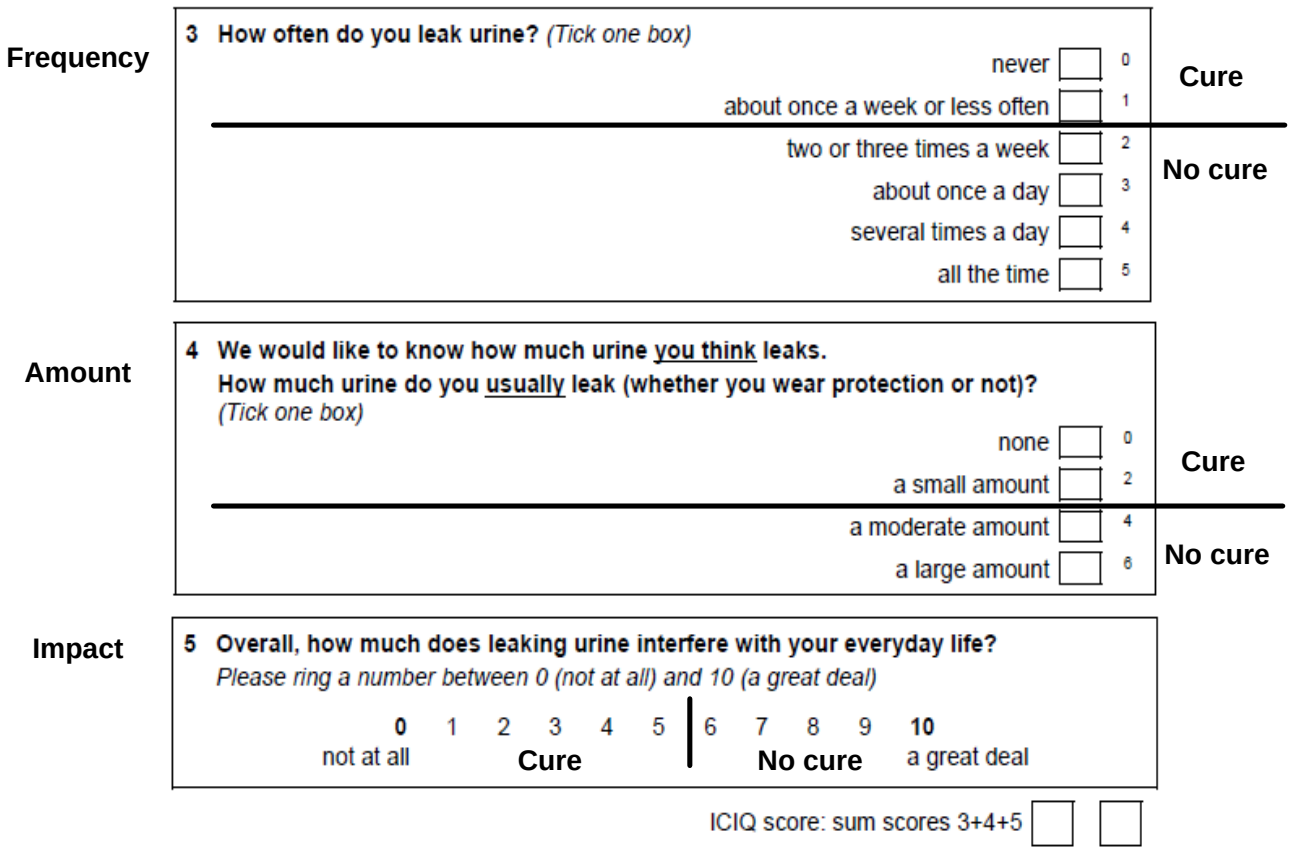
KLEG10= Vaginal urethrocystopexy with use of sling

KLEG10A=Vaginal urethrocystopexy with use of sling through foramen obturatum

KLEG20= Plastic repair of female pelvic floor with levator division

KLEG96= Other vaginal operation for incontinence

10.3 The International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF)



10.4 Hospital contacts within 30 days, International Classification of Diseases (ICD 10)

Main groups	Groups of diagnoses	Diagnose codes
1	DN30* = Cystitis	DN30.0: Acute cystitis DN30.1: Interstitial cystitis (chronic)
	DN32* = Diseases in the bladder, others	DN329: Bladder disorder, unspecified
	DN35* = Strictura urethrae	DN393: Stress incontinence DN394: Other specified urinary incontinence DN394.C Other specified urinary incontinence, urgency
	DN39* = Diseases in urinary tracts, others	
2	DN810*=Urethrocele feminae	
3	DR30*= Dysuria DR319*= Hematuria DR33* = Urinary retention DR35* = Polyuria DR391 = Voiding difficulties DR393 = Pollakisuria	DR339: Disorder of urinary system, unspecified DR339C: Retention of urine
4	DZ090= Control	DZ090 Control after operation/ another condition
5	Miscellaneous	DR100 Acute abdomen DR108 Abdominalia, not specified DL029C Abscess cutis DM545 Lower back pain DN939 Abnormal uterine and vaginal bleeding DT889 Complication of surgical and medical care, unspecified DT983 Sequelae after medical treatment DVRK01:Perioperative bleeding

10.5 Patient characteristics related to surgeon –and department volume, 2007-2011, Denmark

Variables	Surgeon volume				Department volume		
	0-25[2]	26-75[2]	> 75[2]	p-value	0-15[2]	>15[2]	p-value
Age, years, mean (SD)	66.5 (13.1)	64.8 (13.9)	63.5 (14.2)	0.07	63.0 (15.0)	65.4 (13.2)[8]	0.02
BMI, mean (SD)	28.2 (6.4)	27.2 (5.6)	26.3 (4.9)	0.002	28 (6.4)	26.2 (4.7)	0.001
Type of UI							
Stress	33/85(38.8)	24/101(23.7)	103/323(31.9)	0.3	54/170(31.8)	115/375(30.7)	0.52
Urgency	5/85 (5.8)	9/101 (8.9)	17/323 (5.2)		9/170 (5.3)	29//375 (7.7)	
Mixed	43/85 (50.6)	64/ 101 (63.4)	183/ 323 (56.7)		99/170 (58.2)	205/375 (54.7)	
Not specified	4/85 (4.7)	4/ 101 (3.9)	20/323 (6.2)		8/170 (4.7)	26/375 (6.9)	
Smoking	18/74 (24.3)	17/91 (18.7)	61/317 (19.2)	0.58	36/156 (23.1)	64/349 (18.3)	0.22
Alcohol units per week, mean(SD)	2.3 (4.0)	2.8 (4.5)	2.7 (4.3)	0.78	2.7 (4.3)	2.8 (4.4)	0.71
ASA							
1-2	64/ 86 (74.4)	82/98 (83.7)	272/301 (90.3)	0.001	138/172 (80.2)	289/324 (89.2)	0.006
3-5	22/86 (25.6)	16/98 (16.3)	29/301 (9.6)		34/172 (19.8)	35/324 (10.8)	
Parity, mean (SD)	2.3 (1.2)	2.2 (1.3)	2.3 (1.2)	0.31	2.1 (1.2)	2.3 (1.2)	0.03
Previous surgery							
Hysterectomy	34/91 (37.4)	29/107 (27.1)	104/330 (31.5)	0.30	57/179 (31.8)	123/380 (32.4)	0.90
UI surgery	17/92 (18.5)	19/108 (17.6)	60/326 (18.4)	0.98	28/180 (15.6)	73/378 (19.3)	0.28
POP surgery	15/90 (16.7)	20/105 (19.0)	64/326 (19.6)	0.82	34/177 (19.2)	72/377 (19.1)	0.98
Use of preoperative medication							
Oestrogen	84/119(70.6)	92/133 (69.2)	268/439 (61)	0.02	159/258(61.6)	324/491 (65.9)	0.23
Ant muscarinic drugs	84/ 119(70.6)	38/133(28.5)	109/439 (24.8)	0.46	63/258 (24.4)	125/491 (25.5)	0.76
Diuretics	62/119 (52.1)	56/ 133(42.1)	174/439 (39.6)	0.02	114/258 (44.2)	204/491 (41.6)	0.49
Other drugs	4/119 (3.4)	5/133 (3.8)	27/439 (6.2)	0.25	9/258 (3.5)	32/491 (6.5)	0.08

[1]Number/total of women (%), n = 731, unless stated otherwise.

[2]Number of urethral injections performed by the surgeon or annually by the department

BMI body mass index, *ASA* American Society of Anaesthesiologists' Classification, *UI* Urinary incontinence *POP* Pelvic organ prolapse .Other drugs decompressing, imipramine or duloxetine

10.6 Cochrane- analysis

Analysis 1.26. Comparison 1 Transobturator (TOR) versus retropubic route (RPR), Outcome 26 Repeat incontinence surgery (short term, ≤ 1 year).

Review: Mid-urethral sling operations for stress urinary incontinence in women

Comparison: 1 Transobturator (TOR) versus retropubic route (RPR)

Outcome: 26 Repeat incontinence surgery (short term, ≤ 1 year)

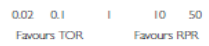
Study or subgroup	TOR n/N	RPR n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Andonian 2007	2/77	0/80		3.5 %	5.19 [0.25, 106.44]
Barber 2008	1/75	4/85		26.8 %	0.28 [0.03, 2.48]
David-Montefiore 2006	0/46	0/42			Not estimable
Deffieux 2010	1/69	2/69		14.3 %	0.50 [0.05, 5.39]
Laurikainen 2007	1/131	2/134		14.2 %	0.51 [0.05, 5.57]
Riva 2006	2/65	0/66		3.6 %	5.08 [0.25, 103.73]
Ross 2009	7/86	5/95		34.0 %	1.55 [0.51, 4.69]
Schierlitz 2008	7/82	0/80		3.6 %	14.64 [0.85, 252.13]
van Leijsen 2013	0/90	0/30			Not estimable
Total (95% CI)	**721**	**681**		**100.0 %**	**1.64 [0.85, 3.16]**

Total events: 21 (TOR), 13 (RPR)

Heterogeneity: $Chi^2 = 7.77$, $df = 6$ ($P = 0.26$); $I^2 = 23\%$

Test for overall effect: $Z = 1.48$ ($P = 0.14$)

Test for subgroup differences: Not applicable

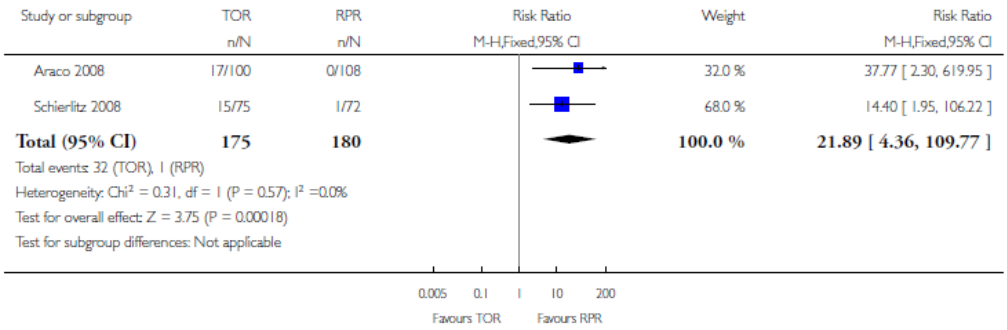


Analysis 1.27. Comparison 1 Transobturator (TOR) versus retropubic route (RPR), Outcome 27 Repeat incontinence surgery (medium term , 1 to 5 years).

Review: Mid-urethral sling operations for stress urinary incontinence in women

Comparison: 1 Transobturator (TOR) versus retropubic route (RPR)

Outcome: 27 Repeat incontinence surgery (medium term , 1 to 5 years)

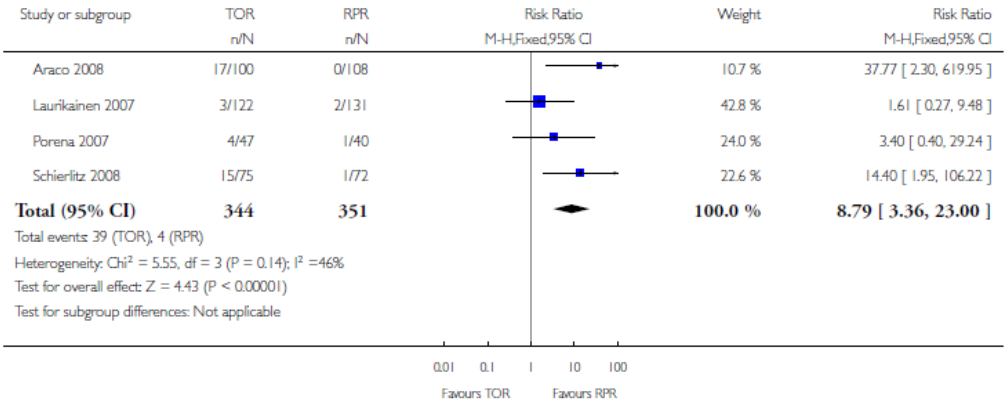


Analysis 1.28. Comparison 1 Transobturator (TOR) versus retropubic route (RPR), Outcome 28 Repeat incontinence surgery (long term > 5 years).

Review: Mid-urethral sling operations for stress urinary incontinence in women

Comparison: 1 Transobturator (TOR) versus retropubic route (RPR)

Outcome: 28 Repeat incontinence surgery (long term > 5 years)



11. Articles

GYNECOLOGY

Reoperation for urinary incontinence: a nationwide cohort study, 1998–2007

Margrethe Foss Hansen, MD; Gunnar Lose, MD, DMSc; Ulrik Schiøler Kesmodel, MD, PhD; Kim Oren Gradel, DVM, PhD

BACKGROUND: The synthetic midurethral slings were introduced in the 1990s and were rapidly replaced the Burch colposuspension as the gold standard treatment for urinary incontinence. It has been reported that the retropubic midurethral tape has an objective and subjective cure rate of 85% at 5 years of follow-up, but the rate of reoperation after retropubic midurethral tape at the long-term follow-up is less well described. The existing literature specifies an overall lifetime rate of reoperation of about 8-9% after an initial operation for urinary incontinence. There are, however, conflicting statements about the risk of reoperation after specific surgical procedures for urinary incontinence.

OBJECTIVE: The objective of the study was to describe the cumulative incidence of reoperation within a 5 year period after different types of surgical procedures for urinary incontinence based on a nationwide population.

STUDY DESIGN: We used the Danish National Patient Registry to identify women who had surgery for urinary incontinence from 1998 through 2007 and the outcome was a reoperation within 5 years. Kaplan-Meier curves were used to estimate the rate of reoperation for 6 types of surgery for urinary incontinence (retropubic midurethral tape, transobturator tape, urethral injection therapy, Burch colposuspension, pubovaginal slings, and miscellaneous operations). Cox proportional hazard models were used to estimate the hazard ratio (HR) with 95% confidence intervals (CIs), adjusted for factors suspected to be associated with reoperation.

RESULTS: A total of 8671 women (mean age, 56.1 years, range 6.7–93.7 years) underwent surgical treatment for urinary incontinence. Among these women, 5820 (67%) received a synthetic midurethral sling at baseline. The cumulative incidence of reoperation after any surgical treatment for urinary incontinence was 10%. The lowest rate of reoperation was observed among women having pubovaginal slings (6%), retropubic midurethral tape (6%) and Burch colposuspension (6%) followed by transobturator tape (9%), and miscellaneous operations (12%), whereas the highest observed risk was for urethral injection therapy (44%). In a Cox proportional hazard model that adjusted for age, department volume, and calendar effect, the transobturator tape carried a 2-fold higher risk of reoperation (HR, 2.1; 95% CI, 1.5–2.9), and urethral injection therapy carried a 12 fold-higher risk (HR, 11.5; 95% CI, 9.3–14.3) compared with retropubic midurethral tape.

CONCLUSION: This nationwide cohort study provides physicians with a representative evaluation of the rate of reoperations after surgical procedures for urinary incontinence. Pubovaginal slings, Burch colposuspension, and retropubic midurethral tape had a similar risk of reoperation (6%). Women who were operated with transobturator tape had a significantly higher risk of reoperation compared with retropubic midurethral tape.

Key words: reoperation, repeat surgery, retropubic midurethral tape, transobturator tape, urinary incontinence

The synthetic midurethral slings (such as retropubic midurethral tape, transobturator tension-free vaginal tape, and transobturator tape) are now the gold standard treatment for urinary incontinence (UI). They were introduced in the 1990s and rapidly replaced the Burch colposuspension as the new standard because of the minimal invasive approach, which had the advantage of technical ease, shorter operative times, and the ability to be performed on an ambulatory basis.[1]

It has been reported that retropubic midurethral tape has an objective and subjective cure rate of 85% at 5 years of follow up.[2,3] Only 3 register-based studies, however, have used reoperation after retropubic midurethral tape as an outcome for the long-term follow-up (5–10 years).[3-5] Existing literature specifies an overall lifetime rate of reoperation of approximately 8-9% after an initial operation for UI.[1] There are, however, conflicting statements about the risk of reoperation after specific surgical procedures for UI.[6,7] It is well documented that urethral injection therapy has a high rate of repeat surgery, but there is no comparative study on the risk of reoperation after retropubic midurethral tape and transobturator tape based on a nationwide population.[1,7]

The synthetic midurethral slings (MUS) have shown similar safety and efficiency, and according to a Cochrane study based on short- and medium-term follow-up, the risk of reoperation is also similar for retropubic midurethral tape and transobturator tape.[8] Nevertheless, a few studies have shown a significantly higher risk of reoperation after transobturator tape compared with retropubic midurethral tape.[9-11] The primary objective of this study was to describe the 5 year incidence of reoperation after different surgical procedures for UI based on a nationwide population.

Materials and Methods

Study setting

In Denmark, the health care system is tax financed and provides health care free of charge for all residents.[12] The initial medical contact is with the general practitioner, who may refer the patient to a public or private hospital.

Data source

Because the Danish unique civil registration number (CPR number) enables

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linkage between all nationwide registers, the entire Danish population can be considered a cohort.

The Danish National Patient Registry was established in 1977 and provides information on diagnoses, minor procedures, and operations of inpatients, outpatient, and emergency room visits in Danish hospitals.[12] It is mandatory by Danish law for all Danish hospital departments and private hospitals to report data to the Danish National Patient Registry. The registry is used for administration, quality of care, and research. Studies of procedure codes registered with the Danish National Patient Registry have shown a high validity.[13-16]

The Danish Civil Registration System was established in 1968 and provides information on gender, date of birth, and continuously updated data on vital status.[17] As a result, patients can be tracked over time with accurate accounting for censoring because of emigration or death.

Subjects

The cohort comprised all female patients recorded in the Danish National Patient Registry as having undergone surgical treatment for UI from 1998 through 2007 and with no surgery for UI 2 years prior to enrollment in the study. This period of 2 years of no exposure was inserted to ensure that no women with recent surgery for UI were included (Figure 1). If 2 or more procedures were registered on the same first-time date of surgery, the observations were excluded from the cohort.

Definition and outcome

The primary objective was to evaluate the cumulative incidence of reoperation after different surgical procedures for UI within 5 years. For all operations we used the Nordic Medico-Statistical Committee procedure codes,[18] which were divided into 6 groups (Appendix A): (1) retropubic midurethral tape (code KLEG10); (2) transobturator tape (code KLEG10A); (3) urethral injection therapy (codes KKDV20 and KKDV22) with polyacrylamide gel or polyacryl hydrogel; (4) pubovaginal slings (code KKDG30), which is an a.m. McGuire procedure performed with autologous fascia (rectus fascia or fascia lata); (5) Burch colposuspension (code KDG00); and (6) miscellaneous operations that separately were less frequently used procedures for UI (codes KDG01, KDG10, KDG31, KDG40, KDG50, KDG96, KDG97, KLEG00, KLEG20, and KLEG96). A reoperation was defined as any subsequent surgical treatment for UI.

Statistical analysis

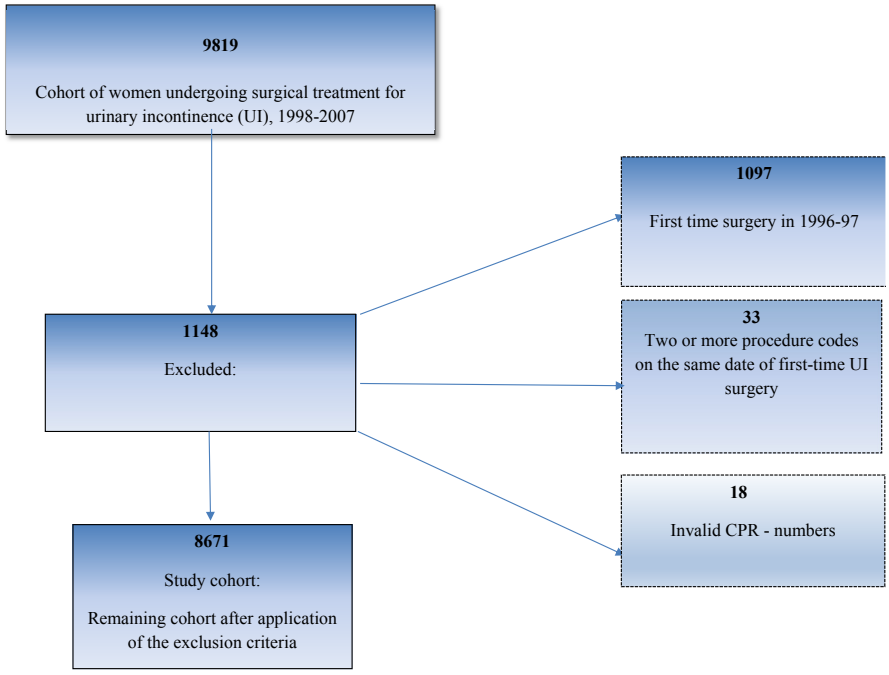
Women with or without reoperation were compared by the χ^2 test and the χ^2 trend test (categorical variables) or the Student's *t* test (age). The start date was set at baseline surgery and an outcome was a reoperation within the following 5 years. A Kaplan-Meier curve was used for measuring the time to reoperation for the 6 groups of surgical treatment. Information on vital status was obtained using the CPR number, and data were censored before time if the women disappeared, emigrated, or died within the 5 year follow-up period.

A Cox proportional regression hazard model assessed the hazard ratio (HR) with 95% confidence intervals (CIs) for each type of procedure (retropubic midurethral tape as the reference group), adjusting for age, department volume, and calendar effect.

To adjust for the department volume, we calculated the annual number of UI procedures for each department and computed tertiles from these. Because we included all surgical procedures for UI since the implementation of the synthetic MUS, we took the initial learning curve for retropubic midurethral tape into account by adjusting for each year (1998−2007) as well as for both periods (1998−2002 and 2003−2007) as a measure of calendar effect. Only results for adjustment for each year are presented because no differences were observed between the 2 modes of adjustment.

Data analysis was performed using Stata version 13.0 (StataCorp, College Station, TX).

FIGURE 1
Derivation of study cohort



CPR, Danish unique civil registration number; *UI*, urinary incontinence.

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Approval

This study was approved by the Danish Data Protection Agency (number 2013-41-2210). Because the study did not include patient contact, it was not necessary to obtain approval from the Health Research Ethics Committee.

Results

A total of 8671 women (mean age 56.1 years, ±12.6) underwent surgical treatment for UI from 1998 through 2007. Among these, 888 women (10%) were reoperated within a 5 year period (Table 1). The lowest rate of reoperation was observed among women who had pubovaginal slings (6%), retropubic midurethral tape (6%), and Burch colposuspension (6%) followed by transobturator tape (9%) and miscellaneous operations (12%), whereas the highest observed risk was for urethral injection therapy (44%).

At baseline, women subsequently undergoing reoperation were significantly older than women not being reoperated (mean age, 58.4 vs 55.9 years) ($P < .001$). However, the difference was present only for women operated with transobturator tape (58.3 vs 53.8 years, $P < .004$) and urethral injection therapy (64.4 vs 61.7 years, $P < .009$).

The number of women who underwent reoperation was significantly increasing from low-volume (6%) over medium-volume (8%) to high-volume departments (12%) (P for trend $< .001$). We stratified this by the 6 groups of surgical treatments, and only women with urethral injection therapy had a higher frequency of reoperation increasing with department volume, whereas no differences were observed for the other treatment modalities.

In the first period (1998–2002), the proportion of retropubic midurethral tapes (35%) was almost equal to Burch colposuspensions (28%), but in the second period (2003–2007), the synthetic MUS had replaced Burch colposuspension in the surgical treatment of UI (81% vs 2%, Table 2). At low-volume departments, transobturator tape (29%) was more frequently used compared with high-volume departments (13%), whereas urethral injection therapy was more rarely used.

The risk of reoperation was determined by the Kaplan-Meier curves for the 6 groups of treatments (Figure 2). The majority of reoperations occurred within the first 2 years of the primary operation and then leveled off during the remaining 3 years. The median time to reoperation was 1 year for sling surgery (retropubic midurethral tape, transobturator tape, and pubovaginal slings), 2 years for Burch colposuspension, and 6 months for urethral injection therapy.

Among women with urethral injection therapy, 30% had repeat UI surgery within the first year and 14% had repeat UI surgery from 2 to 5 years.

Because 4 women emigrated before their primary operation, 8667 women were included in the Cox proportional hazard model. A total of 368 women (4%) were censored before time because of death (n = 345), emigration (n = 22), or disappearance (n = 1).

After adjusting for age, department volume, and calendar effect, the risk of repeat surgery was almost 12-fold higher for urethral injection therapy, and for transobturator tape, the risk of reoperation was significantly higher in comparison with retropubic midurethral tape (HR, 2.1; 95% CI, 1.5-2.9) (Table 3). There was virtually no difference between the crude and adjusted HRs.

Comment

In this nationwide population-based cohort study, we found a cumulative incidence of reoperation of all surgical procedures for UI of 10% within a 5 year period. For retropubic midurethral tape, the incidence of 6% remained stable during the study period (1998–2007) and was thus unlikely to be related to the initial learning curve for retropubic midurethral tape.

An Austrian single center study (n = 101) showed a similar rate of 6% of reoperation after retropubic midurethral tape at 5 years,[3] whereas 2 other studies based on 1 (n = 141) and 2 centers (n = 483), at 10 years of follow up showed an incidence of 7.8% and 2.8%, respectively.[4,5] Two major population-based studies have evaluated reoperation after all types of sling surgery and showed comparable rates of reoperation at 5 years of follow-up (5% and 8%).[1,6]

Significantly, more women from high-volume departments underwent reoperation compared with low-volume departments. However, when stratifying by the 6 groups of surgical treatment, this difference was present only for women treated with urethral injection therapy. Urethral injection therapy is associated with a high rate of reinjections, and this treatment is mainly performed at medium- and high-volume departments in Denmark. For other outcomes, our study indicated no association between department volume and risk of reoperation.

The majority of reoperations occurred within the first 2 years of the primary operation, and this corresponds to other studies.[1,6,7] The median time to

TABLE 1
Baseline characteristics for women in the National Patient Registry having urinary incontinence surgery by reoperation, Denmark, 1998–2007

	Complete cohort (n = 8671)	No reoperation (n = 7783)	Reoperation (n = 888)	*P* value
Age, y, mean ± SD	56.1 (12.6)	55.9 (12.4)	58.4 (14.4)	< .001[a]
Procedures performed, volume				
High, %	5931 (101)[b]	5249 (89)	682 (12)	< .001[c]
Medium, %	2095 (100)	1927 (92)	168 (8)	
Low, %	645 (100)	607 (94)	38 (6)	

[a] Student's t test; [b] Because of rounding, percentages exceed 100; [c] *P* value was based on a χ^2 test statistic of a 3 × 3 frequency table of department volume for surgical procedures for urinary incontinence at baseline.

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TABLE 2
Surgical procedures for urinary incontinence and department volume, 1998–2002 and 2003–2007

Department Volume, %	Period 1998–2002				Period 2003–2007			
	Low (n = 221), medium (n = 519), and high (n = 1820) Total (n = 2560)				Low (n = 424), medium (n = 1576), and high (n = 4111) Total (n = 6111)			
Retropubic midurethral tape, %	56 (25)	102 (20)	731 (40)	889 (35)	289 (68)	1178 (75)	2674 (65)	4141 (68)
Transobturator tap, %[a]	—	—	—	—	122 (29)	149 (10)	519 (13)	790 (13)
Urethral injection therap, %	4 (2)	3 (1)	129 (7)	136 (5)	4 (1)	132 (8)	607 (15)	743 (12)
Colposuspension, %	116 (53)	240 (46)	372 (20)	728 (28)	1 (0)	46 (3)	56 (1)	103 (2)
Pubovaginal slings, %	1 (1)	55 (11)	178 (10)	234 (9)	0 (0)	57 (4)	110 (3)	167 (3)
Miscellaneous, %	44 (20)	119 (23)	410 (23)	573 (22)	8 (2)	14 (1)	145 (4)	167 (3)

[a] Blank cells: transobturator tape was first implemented in 2003 in Denmark, and therefore, no data appear in these cells (1998–2003).

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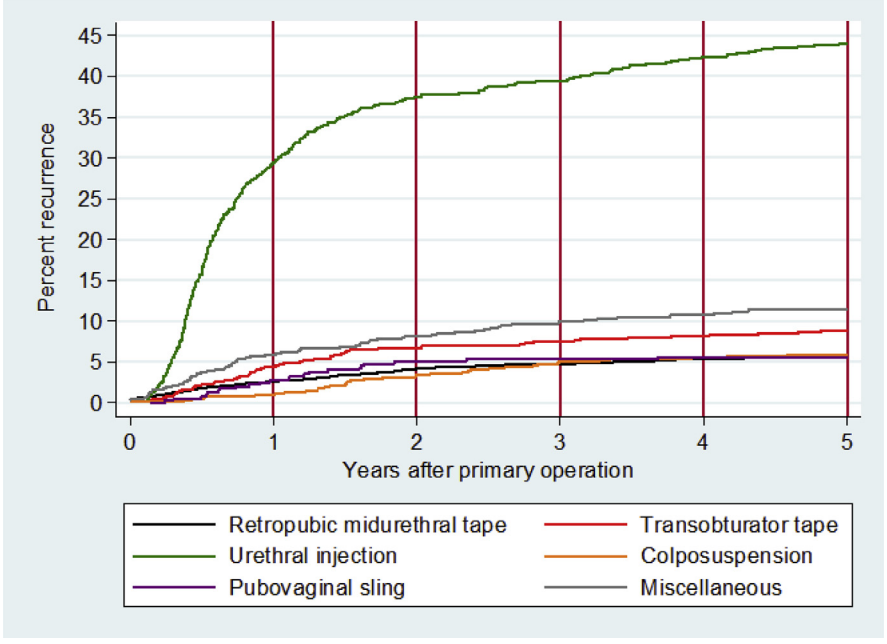
reoperation was 1 year for all sling surgeries (retropubic midurethral tape, transobturator tape, and pubovaginal slings) and urethral injection therapy, whereas it was 2 years for the Burch colposuspension. This might reflect the fact that surgeons are probably more reluctant to perform new surgery after major surgery in comparison with minimal invasive procedures.[1] The median time for repeat surgery after urethral injection therapy was 6 months, and similarly, the threshold for receiving more than 1 treatment might be lower because of its minimal invasiveness.

We found a rate of repeat surgery for urethral injection therapy of 30% within the first year, and this is similar to the literature because two to three injections are likely to achieve a satisfactory result.[19] As expected, urethral injection therapy also had the highest rate of repeat surgery, and this corresponds to previous reports.[1,7]

Our observation that transobturator tape was associated with a significantly higher risk of reoperation is novel in the literature. A Cochrane study (2009) concluded, based on short- and medium-term follow-up, that there was no statistically significant difference in the risk of reoperation between retropubic midurethral tape and transobturator tape (RR, 1.52; 95% CI, 0.90–2.59).[8]

In our study, compromising 5820 women, the HR for reoperation after transobturator tape compared with retropubic midurethral tape (HR, 2.1; 95% CI, 1.5–2.9) was comparable with their results. In contrast to our study, the Cochrane study included only 746 women, and the follow-up period did not extend beyond 12 months.[20-24]

FIGURE 2
Kaplan-Meier survival curve after surgical treatment of urinary incontinence at baseline



This survival curve depicts the cumulative incidence of reoperation after 6 surgical procedures for urinary incontinence. The table lists the incidence of reoperation after data were censored for death, emigration, and disappearance at years 1–5.

Colpo, Burch colposuspension; *Pubovag*, pubovaginal slings; *TOT*, transobturator tape; *TVT*, tension-free vaginal tape.

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TABLE 3
Cox proportional hazard regression analysis for time to repeat urinary incontinence surgery

	Hazard ratio (95% CI), reoperation	Adjusted hazard ratio (95% CI), reoperation[a]
Procedures		
Retropubic midurethral tape	(Reference)	(Reference)
Transobturator tape	1.7 (1.3–2.3)	2.1 (1.5–2.9)
Urethral injection therapy	10.7 (8.9–12.8)	11.5 (9.3–14.3)
Colposuspension	1.3 (0.9–1.8)	1.4 (1.0–2.0)
Pubovaginal slings	1.1 (0.8–1.9)	1.2 (0.7–1.9)
Miscellaneous	2.2 (1.6–2.8)	2.1 (1.5–2.8)

CI, confidence interval.

[a] Adjusted for age, department volume, and calendar effect (1998–2002 and 2003–2007).

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In the recent Cochrane study (2014), the results of the study also showed no statistical difference in the risk of reoperation between retropubic midurethral tape and transobturator tape (RR, 1.26; 95% CI, 0.81–1.95).[25]

The cure rate of the retropubic midurethral tape and transobturator tape is based on short- and medium-term follow-up well documented to be similar, whereas it is generally believed that women with more severe incontinence (or intrinsic sphincter deficiency) are more successful with the retropubic midurethral tape owing to its more obstructive character.[10,21,26] It is very likely that only women with severe UI are reoperated. A reoperation is therefore a fairly hard outcome measure, and it is in this comparison that retropubic midurethral tape proves to be superior to transobturator tape. Even if women with more severe UI receive a retropubic midurethral tape, the adjusted risk of reoperation is still half the risk compared with transobturator tape, and hence, retropubic midurethral tapes stand the test of time. Our study thus indicates that retropubic midurethral tapes per se are more efficient than transobturator tapes.

However, we also tested other assumptions to explain the difference in the risk of reoperation between retropubic midurethral tape and transobturator tape. Our results showed that women reoperated with transobturator tape were significantly older than women not reoperated, and this was not found with retropubic midurethral tape. This could pose a selection bias and hence explain the higher risk of reoperation among women with transobturator tape.[9] However, after adjusting for age, the risk of reoperation was unaltered, suggesting that the risk is mainly due to factors other than age.

It is well documented that there is a learning curve for synthetic MUS, and a certain amount of surgeon volume is necessary to maintain skills.[27,28] Because a relatively high proportion of operations with transobturator tape was performed at low-volume departments, we assumed that the higher risk of reoperation after transobturator tape might be due to less surgeon skills at those places. Still, there was no effect on the rate of reoperation after adjusting for department volume. Even so, it is reasonable to assume that department volume and surgeon volume are positively correlated. Further impact of surgeon skills could not be tested with our data.

A final assumption was that transobturator tape came later on the market and that surgeons therefore were less familiar with transobturator tape. It is, however, unlikely that a higher incidence of reoperation should be related to the initial learning curve for transobturator tape because the risk of reoperation after transobturator tape remained stable for both the transobturator tape (2003–2007) and the retropubic midurethral tape (1998–2007).

The lowest rate of reoperation was observed for retropubic midurethral tape, pubovaginal slings, and Burch colposuspension. Both Burch colposuspension and retropubic midurethral tape have shown to be effective in the treatment of UI, and in our study the risk of reoperation was similar.[2] Prior studies have reported conflicting results regarding differences in reoperation rates between sling surgery and Burch colposuspension.

Two major register-based studies by Jonsson Funk et al[1] (n = 155,458) and Fialkow et al[6] (n = 41,000) showed an increased risk of repeat surgery after sling surgery, whereas a minor study by Abdel-Fattah et al[7] (n = 762), showed the opposite. However, these studies did not compare Burch colposuspension with the retropubic midurethral tape but to a heterogeneous group of slings. The risk of reoperation after tension-free vaginal tape (TVT) and pubovaginal slings was found to be similar in our study, and this corresponds with the current literature.[8]

We contribute to the current literature with a comparative study on reoperation after retropubic midurethral tape and transobturator tape based on an entire nation because previous population-based studies have not differentiated between sling types.[1,6,7] Nevertheless, our results do not apply to any exact TVT or transobturator tape because many different synthetic MUSs are now available. The present study supports the contention that not all slings are equal, and as still more devices are available on the market, it seems critically important that future studies report not only efficiency and safety for a product but also long-term outcomes including the risk of reoperation. This study emphasizes the need for register-based studies to be conducted because a larger sample size and longer follow-up is usually obtained in comparison with randomized controlled trials.

The strengths of our results relate to the robust information in the registry we used. Because studies of procedure codes, registered with the Danish National Patient Registry, have shown a positive predictive value of 93.6—99 %,[13-15] the current UI procedure codes registered with the Danish National Patient Registry are supposed to have a correspondingly high positive predictive value.

Because the present study is based on a nationwide population and includes both public and private hospitals, the analyses might be more generalizable. Some previous studies were based on data from privately insured patients, and therefore, generalizability was lower because a large group of elderly, chronically ill, and/or socially disabled might be excluded.[1,6] Because we included all women since the implementation of the synthetic MUS (1998) in Denmark, we obtained a large material on sling surgery. Furthermore, we were able to account for the specific time that each woman was enrolled in the registry and thus able to use person-time contribution and survival methods, which allowed us to identify reoperations for up to 5 years. In addition, the censoring of women who died or migrated made our follow-up on reoperations after surgical treatment for UI more accurate.

However, there were several limitations of this study, which warrant further discussion. We were not able to include other potential risk factors related to reoperation, such as body mass index, severity of UI symptoms, or surgeon skills. We also lacked information on the synthetic MUS, whether they were exited or placed over an existing MUS and for which reasons they were removed (eg, overactive bladder or erosion). However, such clinical variables will be available in the future because the database completeness for the Danish Urogynaecological Database and other international clinical databases have improved over time.

Insertion of a 2 year period without exposure ensured that no women with recent surgery were included. However, we cannot rule out that a few women had surgical treatment for UI prior to this period, but preliminary data from the Danish Urogynaecological Database show that is an extremely little proportion of women who requires a third operation for UI (personal commentary by K.O.G.).

In the comparison between repeat midurethral tape and transobturator tape, we cannot exclude confounding by indication because it is possible that more women with severe UI receive a repeat midurethral tape. This is, however, counteracted by the fact that repeat midurethral tape still proves a significantly lower risk of reoperation compared with transobturator tape.

In conclusion, this nationwide population-based study provides physicians with a representative evaluation of the rate of reoperations after different surgical procedures for UI. Our information that transobturator tape is associated with a significantly higher risk of reoperation compared with retropubic midurethral tape has important implications for both surgeons and patients because they consider surgical options for the treatment of UI. ■

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Appendix

Surgical procedures according to the Danish Nordic Medico-Statistical Committee (NOMESCO)[18]

KDG00 = Retropubic suspension of urethra
KDG01 = Percutaneous endoscopic retropubic suspension of urethra
KDG10 = Abdominovaginal suspension of bladder neck
KDG30 = Suprapubic sling urethrocystopexy
KDG31 = Percutaneous endoscopic suprapubic sling
KDG40 = Suprapubic urethrocystopexy
KDG50 = Transabdominal plastic repair of pelvic floor for UI
KDG96 = Other operation on urethra or bladder neck for incontinence
KDG97 = Other percutaneous endoscopic operation on urethra or bladder neck for incontinence
KDV20 = Submucosal urethral injection
KDV22 = Transluminal endoscopic submucosal urethral injection
KLEG00 = Vaginal urethrocystorrhaphy
KLEG10 = Vaginal urethrocystopexy with use of sling
KLEG10A = Vaginal urethrocystopexy with use of sling through foramen obturatum
KLEG20 = Plastic repair of female pelvic floor with levator division
KLEG96 = Other vaginal operation for incontinence

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ORIGINAL ARTICLE

Repeat surgery after failed midurethral slings: a nationwide cohort study, 1998–2007

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Abstract
Introduction and hypothesis The objective was to describe the choice of subsequent surgery after failure of synthetic midurethral slings (MUS) based on a nationwide background population.
Methods We used the Danish National Patient Registry to identify women who had undergone first-time synthetic MUS from 1998 through 2007. The outcome was repeat surgery with any subsequent procedure code for urinary incontinence within a 5-year period of the first procedure.
Results A total of 5,820 women (mean age 55.4 years, ± 12.1) were registered with a synthetic MUS, and 354 (6 %) underwent reoperation. The first-choice treatment for reoperation was a synthetic MUS (45.5 %) followed by urethral injection therapy (36.7 %) and miscellaneous operations (13.8 %). Pubovaginal slings (2.8 %) and Burch colposuspension (1.1 %) were seldom used. At reoperation, 289 women (82 %) were treated at the department where they had undergone their primary synthetic MUS.
Conclusion In this nationwide cohort study of synthetic MUS a repeat synthetic MUS was the first choice and urethral injection therapy a frequent second choice. The majority of reoperations (82 %) took place in the same department as the primary operation.

Keywords Repeat surgery · Reoperation · Midurethral slings · Tension-free vaginal tape · Transobturator tape

Introduction

Synthetic midurethral slings (MUS) have been the gold standard treatment for women with stress urinary incontinence (SUI) since the late 1990s [1]. Long-term results show that synthetic MUS are safe and effective, but 5–20 % of the women will have recurrence or persistence of urinary incontinence (UI) [2]. As there is currently no consensus on how to manage these women [3–5] the urogynaecologist must base his/her method of treatment on expert opinion or personal experience [3, 4]. The sparsely available literature shows that synthetic MUS represents the mainstay of repeat surgery, but the results are limited to short-term follow-up [6]. There is a variety of surgical treatments, but for most of these approaches there are few data to support their use [3, 6].

The current literature indicates that a relatively small proportion of women will require a second procedure after failure of synthetic MUS [3, 7]. Some international guidelines recommend that repeat surgery after synthetic MUS should be performed at larger centers to ensure that the appropriate expert knowledge is available [7–9].

The primary objective of this study based on a nationwide background population, was to describe the surgical treatment after the failure of synthetic MUS within 5 years of follow-up,

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and secondarily to describe the departmental volume of surgical treatment at reoperation.

Materials and methods

Study setting

In Denmark, the healthcare system is financed by tax and provides care free of charge for the individual patient. Initial contact is with the general practitioner, who may refer the patient to a public or private hospital [10]. Denmark has approximately 5.5 million inhabitants and consists of five regions [10].

At baseline a total of 5,820 synthetic MUS were performed at 42 hospitals during the study period, 5,743 (98.6 %) procedures at public, and 77 procedures (1.6 %) at private hospitals. Every hospital had one Department of Obstetrics and Gynecology. Low-, medium-, and high-volume departments performed 467 (8 %), 1,429 (24.5 %), and 3,924 (67.4 %) synthetic MUS at baseline. Among the high-volume departments, 1,863 out of 3,924 synthetic MUS (47.4 %) were performed at highly specialized departments.

In this study, we refer to a more highly specialized department as one of the five largest departments within each region in Denmark (equivalent to the five largest university hospitals).

Source of data

The Danish National Patient Registry was established in 1977 and provides information on diagnoses, minor procedures, and operations in Danish hospitals [10]. It is mandatory by law for all hospital departments and private hospitals to report to the Danish National Patient Registry. Furthermore, the hospitals have an economic incentive, as they are only reimbursed for the treatment if they report to this registry [10].

The registry is used for administration, quality of care, and research, and studies of procedure codes within the Danish National Patient Registry have shown a high level of validity [11, 12].

Subjects

The core data set comprised all female patients in the Danish National Patient Registry with synthetic MUS from 1998 through 2007 and with no surgical treatment for UI 2 years before enrolment in the study. If two or more procedures were registered on the same date, the observations were excluded from the cohort. We used the NOMESCO procedure codes [13] for synthetic MUS: tension-free vaginal tape (TVT; "KLEG10") and transobturator tape inside-out (TVT-O), transobturator tape outside-in (TOT; "KLEG10A"). For repeat surgery the procedure codes were divided into six groups: TVT ("KLEG10"); TVT-O, TOT ("KLEG10A"); urethral injection therapy ("KKDV20", "KKDV22"), with polyacrylamide gel or polyacryl hydrogel; pubovaginal slings (PVS; "KKDG30"), which is an a.m. McGuire procedure performed with autologous fascia (rectus fascia or fascia lata); Burch colposuspension ("KDG00"); and miscellaneous operations, which separately were less frequently used procedures for UI ("KDG01," "KDG10," "KDG31," "KDG40," "KDG50," "KDG96," "KDG96," "KDG97," "KLEG20," "KLEG96"; see Appendix for details).

Statistical analysis

Descriptive statistics were used to characterize the women undergoing synthetic MUS at baseline and to evaluate the treatment modality and the departmental volume at the primary operation and reoperation. Women with or without reoperation were compared using the Chi-squared test (categorical variables) or Student's *t* test (continuous variables). To evaluate department volume (high, medium, low) for the reoperations we used the Chi-squared test for trend. We calculated the annual number of total UI procedures for each department and computed tertiles from these, which we added to an index for the 10-year study period from which the final tertiles (low-, middle-, and high-volume departments) were computed.

As we included all synthetic MUS carried out since they were implemented in Denmark, we took development into account by dividing the study period into 1998–2002 and 2003–2007.

Data analysis was performed using Stata version 13.0 (StataCorp, College Station, TX, USA).

Approval

The study was approved by the Danish Data Protection Agency (no. 2013-41-2210). As the study did not include patient contact, it was not necessary to obtain approval from the Health Research Ethics Committee.

Results

From 1998 to 2007, 5,820 women (mean age 55.4 ± 12.1 years) had a synthetic MUS for UI, and 354 (6 %) had repeat surgery within a 5-year period (Table 1). Women from low-, medium-, and high-volume departments underwent reoperation to the same extent.

At baseline, 467 synthetic MUS (8 %) were implanted at low-volume, 1,429 (24.6 %) at medium-volume, and 3,924 (67.4 %) at high-volume departments.

Table 1 Baseline characteristics for women with midurethral sling surgery, 1998–2007, Denmark

	Complete cohort	No reoperation	Reoperation	*P* value
Number	5,820	5,466	354	
Mean age	55.4	55.3	56.6	0.06*
Procedures				
Low volume	467	445 (95.3)	22 (4.7)	0.23**
Medium volume	1,429	1,343 (94.0)	86 (6.0)	
High volume	3,924	3,678 (93.7)	246 (6.3)	

*Two-tailed *t* test

**Chi-squared test for trend

Low-volume departments implanted at baseline 122 TOT procedures out of 467 synthetic MUS (26.1 %), which was significantly more than the medium- and high-volume departments who injected 149 out of 1,429 (10.4 %) and 519 out of 3,924 (13.2 %; both $P<0.001$) TOTs respectively (Tables 2, 3).

Women who have repeat surgery subsequent to a TOT were at baseline significantly older than women who were did not undergo reoperation (58.3 vs 53.8 years, $P<0.004$), whereas this difference was not found for TVT (56.2 vs 55.5 years, $P=0.4$).

In the first period (1998–2002), TVT was introduced and the first-choice treatment at reoperation was a new TVT (45.7 %). In the second period (2003–2007) both synthetic MUS had come into use, and in this period a repeat synthetic MUS was still the first choice (45.5 %; Table 4).

It was more common for women with failure of a TVT to have another TVT (37.2 %) rather than the TOT procedure (6.3 %). For TOT, the reverse was observed, as a TOT was preferred (42.0 %) over a TVT (10.4 %). As a second choice, urethral injection therapy was popular during both periods, at 30.4 % and 37.7 %. At reoperation, 289 women (82 %) were treated in the same department where the primary synthetic MUS had been performed; 22 women (7.6 %) in low-volume, 71 women (24.5 %) in medium-volume, and 196 (67.8 %) women in high-volume departments. The remaining 65 women (18 %) had their initial surgery in high-volume departments; 45 of these (69.2 %) were reoperated in highly specialized departments. Low-volume departments offered four different treatments, whereas middle- and high-volume departments used six different treatments (Table 5).

Low-volume departments used TOT in 40.9 % of their repeat surgeries, in contrast to medium- (6.9 %) and high-volume departments, (11.8 %; both $P<0.001$).

Discussion

In our nationwide population-based study of 5,820 women, the cumulative incidence of reoperation within 5 years after synthetic MUS was 6 %.

A synthetic MUS was the first choice for reoperation, which probably reflects the fact that synthetic MUS was also the gold standard for primary surgery. Synthetic MUS, however, remained stable as the first choice of treatment at reoperation in both periods (1998–2002) and (2003–2007), while rapidly increasing as primary surgery in the same period in Denmark and other countries [1, 14, 15].

Two other population-based studies reported a more frequent use of synthetic MUS subsequent to the failure of synthetic MUS [4, 16]. In Taiwan, 64 % of the women underwent a repeat synthetic MUS [16], whereas a study based on the British Society of Urogynecology database showed that 74 % of the women underwent a synthetic MUS as repeat surgery [4].

Women with a failure of primary TOT were more often offered the TOT procedure again rather than a TVT, and vice versa for TVT. There is no evidence to support this practice [3, 4, 17]. However, the sparse literature indicates poorer outcome after a repeat TOT compared with a repeat TVT [2, 18–20].

Not surprisingly, urethral injection therapy was also a frequent choice at reoperation as the main indication is second-line treatment in women not suitable for major UI surgery [21]. In the present study, however, urethral injection therapy was more frequently used (42 %) compared with the UK (14 %) and Taiwan (11 %) [4, 16]. Financial incentives, such as reimbursement, are well-known to affect the overall use of

Table 2 Baseline characteristics for women with tension-free vaginal tape, 1998–2007, Denmark

	Complete cohort	No reoperation	Reoperation	*P* value
Number	5,030	4,745 (94.3)	285 (5.7)	
Mean age	55.6	55.5	56.2	0.39*
Low volume	345	336 (97.4 %)	9 (2.6 %)	0.098**
Medium volume	1,280	1,203 (94.0 %)	77 (6.0 %)	
High volume	3,405	3,206 (94.2 %)	199 (5.8 %)	

*Two-tailed *t* test

**Chi-squared test for trend

Table 3 Baseline characteristics for women with transobturator tape outside-in, 1998–2007, Denmark

	Complete cohort	No reoperation	Reoperation	*P* value
Number	790	721	69	
Mean age	54.2	53.8	58.3	<0.004*
Low volume	122	109 (89.3 %)	13 (10.7 %)	0.91**
Medium volume	149	140 (93.9 %)	9 (5.1 %)	
High volume	519	472 (90.9 %)	47 (9.1 %)	

*Two-tailed *t* test

**Chi-squared test for trend

Table 4 Repeat procedures after failed midurethral slings, 1998–2007, Denmark

	1998–2002						2003–2007					
Baseline	TVT	Urethral injection	Colposuspension	PVS	Miscellaneous	Total	TVT	TOT	Urethral injection	Colposuspension	PVS	Miscellaneous	Total
TVT	21 (45.7)	14 (30.4)	2 (4.4)	3 (6.5)	6 (13.0)	46 (100)	89 (37.2)	15 (6.3)	94 (39.3)	2 (0.84)	4 (1.7)	35 (14.6)	239 (100)
TOT [a]	–	–	–	–	–	–	7 (10.4)	29 (42.0)	22 (31.9)	0 (0.0)	3 (4.4)	8 (11.6)	69 (100)
Total	21 (45.7)	14 (30.4)	2 (4.4)	3 (6.5)	6 (13.0)	46 (100)	96 (31.2)	44 (14.3)	116 (37.7)	2 (0.7)	7 (2.3)	43 (14.0)	308 (100)

TVT tension-free vaginal tape, *TOT* transobturator tape, *PVS* pubovaginal slings

[a] Blank cells: transobturator tape was first implemented in 2003 in Denmark and therefore no data appear in these cells (1998–2003)

specific procedures [22]. As the material for urethral injection therapy is relatively expensive in comparison to kit for synthetic MUS, it is possible that financial aspects also play a role in the choice of repeat surgery. In Denmark, surgical treatment is free of charge for the individual patient, whereas in Britain reimbursement for urethral injection therapy has been predicated only upon the demonstration of severe UI [23]. Regardless of whether economic factors play a role in the choice of subsequent treatment, our results indicate that the approach at reoperation in Denmark is more conservative compared with the UK and Taiwan.

Finally, Burch colposuspension and PVS were a seldom choice at reoperation, which was also observed in Britain [4], and this probably reflects that both treatments are rarely used as primary surgery for UI. In Taiwan, Burch colposuspension and PVS were frequent choices as repeat surgery after a failed synthetic MUS, and this is probably also because of their higher use as primary UI surgery in Taiwan [16].

To the best of our knowledge, the studies from the UK and Taiwan based on a material on repeat surgery ($n=313$) and ($n=170$) comparable with our data ($n=354$) are to date the two only nationwide studies that have reported on recurrent or persistent UI after failed MUS [4, 16]. As there is currently little knowledge on which procedures are used, it is difficult to assess and discuss which procedures should be used after the failure of synthetic MUS [3].

It was remarkable that the majority of women had repeat surgery in the same department where they had undergone primary MUS (82 %), as the Danish Health and Medicines Authority (DHMA) has previously recommended, and the Danish Society of Obstetrics and Gynaecology currently recommends complicated cases to be referred to a more highly specialized department [24, 25].

In fact, in the upcoming plan for specialized functions with all specialties, the DHMA clearly recommends that recurrent or persistent UI after synthetic MUS are to be treated as a highly specialized function, meaning centralization to a few departments [25]. The present study cannot definitely state that repeat surgery after failed synthetic MUS is best managed in highly specialized departments, although some factors indicate this.

First, relatively few women (6 %) had repeat surgery following synthetic MUS and thus most departments have limited experience in this field. It therefore seems reasonable to refer reoperations after synthetic MUS to departments with appropriate expertise within the field of urogynecology [14, 24, 26]. Second, this will also ensure that technical equipment for urodynamics is available, as a thorough evaluation of a patient with failed previous UI surgery should be performed [7–9, 24, 27]. Third, our study showed that high-volume departments offered more surgical treatments in comparison to low-volume departments. This is supported by the fact that surgical treatment modalities for UI at baseline in low-volume departments are also

Table 5 Repeat surgery and department volume, 1998–2007, Denmark

	TVT ($n=117$)	TOT ($n=44$)	Urethral injection ($n=130$)	Colposuspension ($n=4$)	PVS ($n=10$)	Miscellaneous ($n=49$)	Total ($n=354$)
Low-volume department	7 (31.8)	9 (40.9)	5 (22.7)	–	–	1 (4.5)	22 (100)
Medium-volume department	38 (44.2)	6 (6.9)	34 (39.5)	2 (2.3)	1 (1.2)	5 (5.8)	86 (100)
High-volume department	72 (29.2)	29 (11.8)	91 (37.0)	2 (0.8)	9 (3.7)	43 (17.4)	246 (100)

TVT tension-free vaginal tape, *TOT* transobturator tape, *PVS* pubovaginal slings

more limited [15]. Our previous study showed that PVS as primary surgery were not part of the standard assortment in low-volume departments [15], and this study also shows that they were not used as repeat surgery after synthetic MUS. Urethral injection therapy was similarly rarely used at baseline in low-volume departments—more exactly eight urethral injections from 1998 to 2007 [15]. It has been documented that there is a poorer subjective outcome in departments conducting fewer than 15 urethral injection therapies per year [28] and similarly a poorer subjective outcome for a surgeon who has performed fewer than 40 injections [29].

There is therefore a high risk of urethral injection therapy being performed as repeat surgery in low-volume departments by a surgeon who is not doing this procedure routinely.

It seems inappropriate if the choice of surgical options is dependent on which surgical equipment is available at the department or on the surgeon's ability to perform a surgical procedure.

Last but not least, low-volume departments had a predilection for the TOT procedure, as TOT was significantly more used at baseline and at reoperation in comparison to medium- and high-volume departments. A repeat TOT is associated with poorer results and is a practice that is not evidence-based [2, 18–20].

This study provides a representative overview of treatment modality following failure of synthetic MUS based on a nationwide population. Two previous national studies also reported on subsequent treatment following failed MUS. The UK study was, however, limited by its design as a cross-sectional study [4] and did not take the development of synthetic MUS into account, as we did, by including all MUS since the implementation in 1998 in Denmark. The generalizability to a European setting in the study from Taiwan was lower, as data was to a high degree based on privately insured patients [16].

The strengths of our study relate to the robust registry information we used. As it is mandatory by law to report to the Danish National Patient Registry, a high level of data completeness was obtained in the present study. Furthermore, studies of procedure codes for nonmalignant gynecological conditions registered in the Danish National Patient Registry showed a positive predictive value of 94–99 % [11, 12] and therefore the current UI procedure codes should have a correspondingly high positive predictive value.

A major limitation of the study is that we had no results on the number of women with failed synthetic MUS who had conservative treatment (e.g., pelvic floor muscle training, life style advice) and among surgical treatments we had no information on excisions of previous MUS vs placing over an existing MUS. Another limitation was the lack of information on surgeon experience. This will be possible to assess in the future as the Danish Urogynecological Database (DugaBase) and other large national databases evolve [4, 16, 30].

In conclusion, this nationwide study provides an overview of the current surgical management of failure after synthetic MUS. Even though we lack evidence for the best treatment [7–9], the present study showed that the majority of women (82 %) underwent repeat synthetic MUS in the same department in which their primary surgery was performed. It would be appropriate to refer women with synthetic MUS to more specialized departments, as long as we are lacking the standardization of failure management of synthetic MUS, and this is in line with the upcoming recommendation from the DHMA [25]. However, further studies are needed to explore the outcomes after repeat synthetic MUS and how the treatment is best maintained.

As relatively few women receive a repeat synthetic MUS, it seems important that experience within this field is gathered in fewer hands to obtain sufficient knowledge on the failure of synthetic MUS. Furthermore, it is important for a thorough evaluation of a woman with failed synthetic MUS to be performed, and for a wider range of treatment options to be available in the department.

Compliance with ethical standards

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Conflicts of interest Margrethe Foss Hansen had her fee for the conference paid by NUGA, and by the ICS (ICS Travel Award Price 2015), and conference and travel expenses for the EUGA Leading Lights in Urogynaecology, Warsaw, were paid by Astella. Gunnar Lose had research grants from Astellas Pharma (research cooperation with Coloplast under a grant from Advanced Technology Foundation) and a consulting fee from Contura.

Appendix

Surgical procedures according to the Danish Nordic Medico-Statistical Committee (NOMESCO):

KDG00	Retropubic suspension of the urethra
KDG01	Percutaneous endoscopic retropubic suspension of the urethra
KDG10	Abdominovaginal suspension of the bladder neck
KDG30	Suprapubic sling urethrocystopexy
KDG31	Percutaneous endoscopic suprapubic sling
KDG40	Suprapubic urethrocystopexy
KDG50	Transabdominal plastic repair of the pelvic floor for UI
KDG96	Other operation on the urethra or bladder neck for incontinence
KDG97	Other percutaneous endoscopic operation on the urethra or bladder neck for incontinence
KDV20	Submucosal urethral injection
KDV22	Transluminal endoscopic submucosal urethral injection
KLEG00	Vaginal urethrocystorrhaphy
KLEG10	Vaginal urethrocystopexy with use of sling
KLEG10A	Vaginal urethrocystopexy with use of sling through the foramen obturatum
KLEG20	Plastic repair of the female pelvic floor with levator division
KLEG96	Other vaginal operation for incontinence

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A national population-based cohort study of urethral injection therapy for female stress and mixed urinary incontinence - The Danish Urogynaecological Database, 2007-2011

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Abstract

Background:

Urethral injection therapy (UIT) has been performed since the early 20th century and a variety of agents have been launched but many of these were subsequently retracted from the market due to product related side effects.

Polyacrylamide hydrogel **(**PAGH) was introduced in 2006 and is now widely used as agent. No national population-based studies on PAGH have previously been conducted. Furthermore, patient characteristics associated with lower cure are not well-understood.

Objective:

To evaluate the efficacy of PAGH based on a national population during a five-year period (2007-2011) and to examine the influence of patient-related factors, surgeon experience and department volume.

Materials and methods:

Data from the Danish Urogynaecological Database (DugaBase) on women with UIT was used at logistic regression to predict the odds of cure pertaining to patient-related factors, surgeon and department volume on the Incontinence Questionnaire-Short Form (ICIQ-SF) (frequency of UI, amount of leakage and impact of UI on daily life) and the rate of 30-day hospital contacts.

Results:

A total of 731 women were consecutively registered in the DugaBase. Cure was achieved in 75/252 (29.8%) women and no leakage at all in 23/252 (9.1%) at three months follow up. The mean total ICIQ-SF decreased from 16 (SD 3.8) to 10.6 (SD 6.2) ($p < 0.001$).

UIT was performed at 16 departments, of which four high volume departments (> 15 UITs annually) did 547 of 814 UITs (67.2%).

Among patient characteristics the severity of UI decreased the chance of cure in all ICIQ-SF scores (Data not shown). Women who preoperatively used antimuscarinic drugs had a lower chance of cure on the frequency score (adjusted OR 0.14; 95%, CI 0.04-0.41) and the amount score (adjusted OR 0.33; 95%, CI 0.13-0.82). Women treated by a high volume surgeon (> 75 UITs during career as a surgeon) had a higher chance of cure on the frequency score than the low volume surgeon (≤ 25 UITs) (OR 4.51; 95% CI, 1.21-16.82) and a lower risk of 30-day hospital contacts (OR 0.27; 95% CI 0.09-0.76).

Conclusion:

This national population-based cohort study represented cure among women who had UIT in an everyday life setting. The severity of UI was a strong predictor lower cure and similarly a use of antimuscarinic drug preoperatively indicating lower cure for women with severe MUI and UUI. A learning curve for UIT was indicated and that the treatment should be restricted to fewer hands to improve the surgical education and consequently cure for women with UIT.

Introduction

Urethral injection therapy (UIT) has been performed since the early 20th century and a variety of agents have been launched, but many of these were subsequently retracted from the market due to product related side effects [1]. It is an attractive alternative to synthetic midurethral slings (MUSs) for female urinary incontinence (UI) due to its minimal invasive nature and few and mild side effects [2].

Polyacrylamide hydrogel (PAGH) introduced in Europe as a bulking agent in 2006, is now widely used [3]. The current knowledge on UIT with PAGH is based on ten studies with a follow-up of one to three years [4-13] four of which are larger studies [4,8,11,12]. However, no national population-based studies on PAGH have been conducted and there is a lack of studies, which reflects the patient in the daily clinic [14]. Furthermore, patient characteristics associated to lower cure among women injected with PAGH are not well-understood [14].

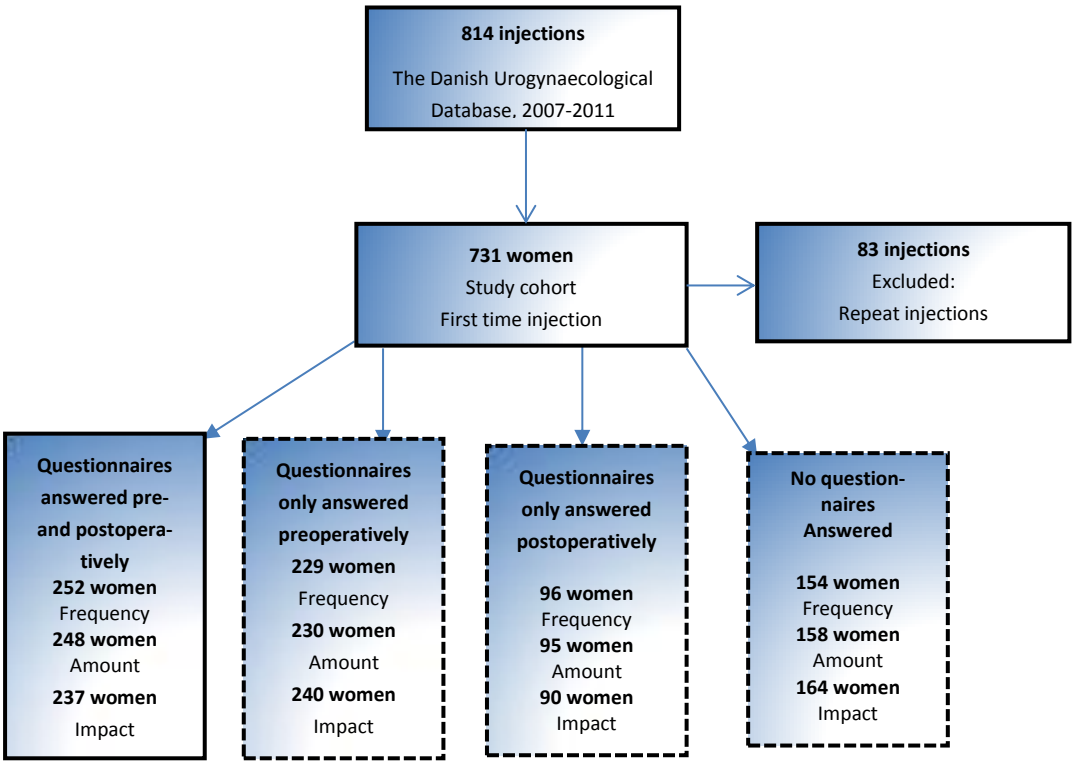
A few studies have indicated that there is a learning curve to master the technique [4,15-17].Two studies have up until now shown that both surgeon and department volume have an influence on the subjective outcomes in UIT [4,16], but no larger studies have assessed these aspects.
The Danish Urogynaecological Database (DugaBase) was established in 2006 to monitor, ensure and improve the quality of urogynaecological surgery [18].This national clinical database poses a unique opportunity to retrieve information on women with UIT as a large population-based sample size from several years can be obtained.
The main purpose of the present study was to evaluate the efficacy of UIT on patient reported outcome measures (PROMs) and the rate of 30 day-hospital contacts based on a national background population during a five-year period (2007-2011). Further, we examined the influence of patient-related factors, surgeon experience and department volume.

Materials and methods

Source of data

Data were retrieved from three Danish registers: DugaBase, the Danish National Patient Registry, and the Register of Medicinal Product Statistics. All Danish residents have a unique personal identification number which incorporates date of birth and gender and is used for all health contacts, thus enabling linkage between all registries. The DugaBase was established as a clinical database in 2006 and serves both clinical and scientific purposes [18-20]. It comprises women residing in Denmark who at the age of 18 or more undergo surgical procedures for UI or pelvic organ prolapse (POP) according to the NOMESCO procedure codes [21]. Since its establishment pre-and postoperative questionnaires have been collected systematically. These include the Incontinence Questionnaire-Short Form (ICIQ-SF) which has been translated but not validated in Danish [19] and the Patient´s Global Impression of Improvement (PGI-I score), which was added in 2013 [20].

Figure 1 Description of the study cohort



The database completeness of the DugaBase has increased from 33% in 2007 to 91% in 2011, using the Danish National Patient Registry as reference whereas the data completeness constantly during this period has been lower [19,22]. This is mainly due to the fact, that the departments have a heterogeneous way of follow-ups after surgical treatment for UI as some departments routinely follow-up all patients whereas other departments only follow up on complicated patients.

The validity of eleven main variables has been examined and we found 90-100% agreement when comparing information from the database with medical records [18]. The standard of surgical quality is set by the DugaBase steering committee [22].

The Danish National Patient Registry was established in 1977 and provides information on diagnoses, minor procedures, and operations of inpatients, outpatients and emergency room visits in Danish hospitals [23,24]. Studies of procedure codes registered in the Danish National Patient Registry have shown a high validity [25,26].

It is mandatory by Danish law for all Danish hospital departments and private hospitals to report data to the DugaBase and the Danish National Patient Registry [23,24]. Furthermore, the hospitals are only reimbursed if they report to the Danish National Patient Registry [23,24].

The Register of Medicinal Product Statistics was established in 1993, and retrieves information from Danish pharmacies on retrieval of medicinal products [27].

Study population and settings

The Danish healthcare system is tax financed and provides care free of charge for all residents [23,24].
The study population included women of 18 years or older residing in Denmark who had first-time UIT with PAGH from 2007 through 2011, as registered in the DugaBase. To assess that a UIT in 2007 was likely to be the woman's first-time UIT we included 2006 as a lag year. Only women, who had completed the questionnaires pre- and postoperatively, were included in the main analyzes (Fig.1). The guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) were applied [28].

In 2003, PAGH (®Bulkamid) was introduced in Denmark, and in 2006 it had almost replaced the previous agent PAGH (®Aquamid) [3]. In the present study, the predominant agent was PAGH (®Bulkamid) as less than 1.2% (10/814) were other agents. In Denmark, UIT is performed transurethrally using the urethroscope and most often in an outpatient setting [4]. There is in Denmark no formal training in UIT. Routinely, planned follow-up for surgical treatment of UI is in Denmark normally at three months.

Potential predictors

Potential variables associated with the outcome of UIT were patient-related factors, surgeon and department volume.

Patient-related factors

Patient-related factors included a medical history as registered in the DugaBase (age, body mass index (BMI), American Society of Anesthesiologist's (ASA) Classification, previous surgery (hysterectomy, UI surgery, POP) surgery and severity of UI preoperatively using the ICIQ-SF.
Information on preoperative use of medication related to UI was retrieved from The Register of Medicinal Product Statistics (diuretics (ATC C03) antimuscarinic drugs (ATC G04BD), estrogens (ATC G03C) and a group of less frequently used drugs (desmopressin ATC H01BA02, imipramine ATC N06AA02 and duloxetine ATC N06AX21).

Surgeon volume

Surgeon volume as registered in the DugaBase for each UIT was categorized into three groups of surgeon volume (number of UITs performed during the career as a surgeon), low (≤ 25), medium (26-75) and high volume (>75).

Department volume

Department volume was defined as in a previous study, high (≥15 UITs *per* year) and low (<15 *per* year) [4]. The Danish National Patient Registry was used as gold standard to secure that the classification of department volume was based on the actual annual number of UITs. A number of 814 of 1346 UITs were registered in the DugaBase. 16 of these 22 departments were registered in the DugaBase. The remaining six departments contributed with 61 of the 1346 UITs (4.5%). All four high volume departments were registered both in the DugaBase and the Danish National Patient Registry.

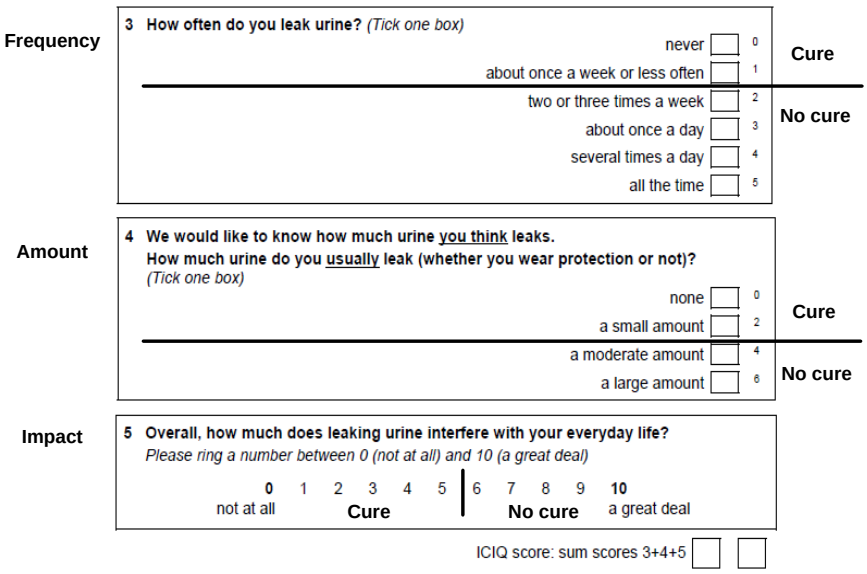
Outcome measures

The primary outcomes were based on the ICIQ-SF, completed at three months follow up after the primary UIT and a secondary outcome was hospital contacts within 30 days.
The ICIQ-SF consists of three questions (frequency of UI, amount of leakage, and impact of UI on the daily life) as well as the sum based on these questions (total ICIQ-SF).
Within each of the three questions "cure" was based on a dichotomization as reported in Figure 2 in accordance with globally accepted criteria reported previously [4-8,12,22].
The steering committee of the DugaBase has defined "cure" (a successful outcome) as leakage once a week or less, often or never and we focused in particular on this outcome [22] and on "no leakage at all" on the frequency score defined as answering never to leakage of urine [5]."Change" was evaluated as the difference on the total ICIQ-SF, pre-and postoperatively.
All relevant hospital contacts to a Department of Obstetrics and Gynaecology with a diagnosis classified according to the International Classification of Diseases, tenth edition (ICD 10) [29] within 30 days from primary UIT, were identified.

Statistical analysis

The first time UIT was the analytical unit. Descriptive statistics was used to evaluate baseline characteristics and outcomes. To evaluate baseline characteristics between patients treated by a low, medium or high surgeon volume, we used the χ^2-test for trend (categorical variables) and one way analysis of variance (ANOVA) (continuous variables) and for department volume the χ^2-test (categorical variables) and the Student´s t-test (continuous variables). Any change from baseline in the ICIQ-SF scores was analysed by the Wilcoxon signed-rank test.

Figure 2 The International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF)



At logistic regression the cure at the ICIQ-SF postoperatively was dichotomized for all three questionnaires and adjusted by the preoperative ICIQ-SF score ("severity").We analyzed the impact of patient-related factors believed to be clinically relevant and the influence of the surgeon and department volume on cure, by uni- and multivariate logistic regression.

Hosmer Lemeshow goodness-of-fit test was calculated to assess the fit of the models.

In sensitivity analysis, we compared potential predictors prior to surgery between women who had filled in both questionnaires pre-and postoperatively on the one hand to women who had not completed the questionnaires (pre- and/or postoperatively) on the other.

A p-value < 0.05 was considered statistically significant.

Data analysis was performed using STATA version 14.0 (StataCorp, College Station, TX USA).

Approval

The study was approved by the Danish Data Protection Agency (J.nr. 2012-41-0414). As the study did not include patient contact, it was not necessary to obtain approval from the Health Research Ethics Committee.

Results

Baseline characteristics

Between January 1st 2007 and December 31st 2011 a total of 731 women with first time UITs were consecutively registered in the DugaBase. Among those, 650 women (88.9%) had one, 79 (10.8%) had two, and 2 (0.3%) had three UITs. The mean age was 64, the mean BMI 26.7 and 56.5% had mixed UI (MUI) and 31% had pure stress UI (Table 1). Patient characteristics related to surgeon and department volume are reported separately (Appendix).

Among the 252 women who pre- and postoperatively had answered both questionnaires, 75 (29.8%) were cured and

Table 1 Patient characteristics for women with first-time urethral injection therapy, 2007-2011, Denmark.

Variables	All[1]
Age, years, mean (SD)	64.0 (13.9)
BMI, mean (SD)	26.7 (5.3) [2]
Type of UI	
Stress	152/490 (31.0)
Urgency	35/490 (7.1)
Mixed	277/490 (56.5)
Not specified	26/490 (5.3)
Smoking	100/505 (19.8)
Alcohol units per week, mean (SD)	2.8 (4.4) [3]
ASA	
1-2	394/458(86.0)
3-5	64/458 (14.0)
Parity, mean (SD)	2.3 (1.2) [4]
Previous surgery	
Hysterectomy	161/505 (31.8)
UI surgery	89/504 (17.7)
POP surgery	91/500 (18.2)
Use of preoperative medication	
Estrogen	422/672 (62.8)
Antimuscarinic drugs	175/672 (26.0)
Diuretics	278/672 (41.3)
Other drugs	36/672 (5.4)

[1] n = 731, unless stated otherwise [2] n = 528 [3] n = 420 [4] n = 564

BMI body mass index, *ASA* American Society of Anesthesiologist's Classification, *UI* Urinary incontinence *POP* Pelvic organ prolapse Other drugs: desmopressin, imipramine or duloxetine

23 (9.1%) achieved "no leakage at all" at three months follow up (Fig. 3). There was a statistical significant improvement on all three scores of the ICIQ-SF (Table 2). The mean total ICIQ-SF score was 16.0 (SD 3.8) and after injection 10.6 (SD 6.2) ($p < 0.001$).

UIT was performed at 16 departments of which four high volume departments performed 547 of 814 UITs (67.2%). There were more UITs performed by high volume surgeons at high volume departments, 368/472 (75.9 %) compared to low volume departments, 117/282 (24.1%), ($p < 0.001$) (data not shown).

Figure 3 Frequency, before and after treatment -based on women who had completed questionnaires both pre- and postoperatively

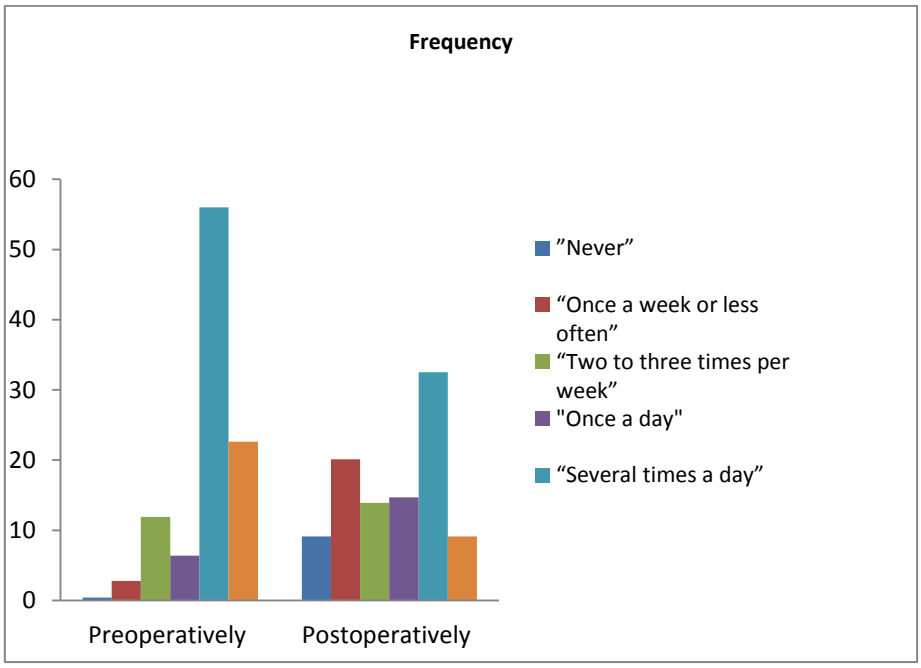


Table 2 Frequency, amount, impact and total score before and after treatment, evaluated by ICIQ-SF -based on women who had completed questionnaires pre- and postoperatively.

ICIQ-SF Questionnaires	Before, (mean± SD)	After (± mean SD)	Change , (± mean SD)	P value [1]
Frequency [2]	3.82 (1.02)	2.68 (1.54)	1.14 (1.49)	0.001
Amount [3]	4.00 (1.62)	2.91 (1.76)	1.08 (1.96)	0.001
Impact [4]	8.10 (2.26)	4.83 (3.58)	3.27 (3.30)	0.001
Total score [5]	16.05 (3.80)	10.58 (6.17)	5.47 (5.66)	0.001

[1] Wilcoxon sign-ranked test[2] n =252[3] n = 248[4] n = 237[5] n = 224

ICIQ-SF The International Consultation on Incontinence Questionnaire Short Form

Patient-related factors

Among patient characteristics, the preoperative severity of UI decreased the likelihood of cure significantly in all scores of the ICIQ-SF (data not shown). Similarly, women with a preoperative use of antimuscarinic drugs had a significantly lower chance of cure on the frequency score (adjusted OR 0.14; 95%, CI 0.04-0.41) and amount score (adjusted OR 0.33; 95%, CI 0.13-0.82) (Table 3).There was no influence SUI, UUI or MUI on cure.

Surgeon volume

Women treated by a high volume surgeon had an increased chance of cure on the frequency score compared to women treated by a low volume surgeon (adjusted OR 4.51; 95% CI, 1.21-16.82), and a lower risk of hospital contacts (adjusted OR 0.35; 95% CI, 0.16-0.79)(Table 4).

Department volume

The risk of hospital contacts was lower for women treated at a high volume department (adjusted OR 0.27; 95% CI 0.09-0.76) (Table 4)

Table 3 Uni- and multivariate analyses of potential predictors for cure, ICIQ-SF (Frequency, Amount and Impact)

Variables	Frequency		Amount		Impact	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
	Odds ratio (95%,CI)	Odds ratio (95%,CI)	Odds ratio (95%,CI)	Odds ratio (95%,CI)	Odds ratio (95%,CI)	Odds ratio (95%,CI)
Age, years	0.98 (0.96-1.00)	0.99 (0.96-1.03)	0.98(0.96-1.00)	0.98 (0.95-1.01)	1.01 (0.98-1.03)	1.02 (0.98-1.05)
BMI, kg/m^2	**0.93 (0.87-0.99)**	0.94 (0.86-1.01)	0.99 (0.93-1.04)	1.01 (0.93-1.08)	0.98 (0.92-1.03)	1.00 (0.94-1.08)
Type of UI						
Stress	Reference	-	Reference	-	Reference	-
Urgency	0.42 (0.12-1.46)		0.65 (0.22-1.93)		1.15 (0.37-3.55)	
Mixed	1.19 (0.63-2.24)		0.96 (0.52-1.78)		1.76 (0.88-3.48)	
Not specified	2.82 (0.70-11.22)		0.55 (0.14-2.12)		0.77 (0.19-3.12)	
ASA						
1-2	Reference	Reference	Reference	Reference	Reference	Reference
3-5	**0.53 (0.33-0.84)**	0.67 (0.34-1.3)	0.67 (0.43-1.05)	0.81 (0.43-1.51)	0.80 (0.50-1.28)	0.80 (0.42-1.51)
Parity	**1.31 (1.03-1.66)**	1.26 (0.97-1.65)	**1.34 (1.07-1.69)**	1.09 (0.84-1.4)	1.11 (0.87-1.42)	1.13 (0.87-1.47)-
Previous surgery						
Hysterectomy	1.18 (0.65-2.12)	1.12 (0.46-2.69)	1.72 (0.92-3.21)	1.44 (0.59-3.48)	1.09 (0.57-2.07)	0.64 (0.27-1.54)
UI surgery	1.21 (0.59-2.46)	1.82 (0.56-5.93)	0.99 (0.45-2.14)	0.62 (0.18-2.09)	0.68 (0.30-1.51)	1.18 (0.37-3.74)
POP surgery	1.07 (0.51-2.26)	0.39 (0.10-1.54)	1.47 (0.65-3.34)	5.62 (1.25-25.32)	0.84 (0.34-2.04)	0.80 (0.21-2.96)
Preoperative medication	0.62 (0.34-1.14)	0.62 (0.25-1.57)	0.55 (0.29-1.00)	0.56 (0.22-1.40)	0.78 (0.41-1.49)	1.12 (0.46-2.7)
Oestrogen	**0.34 (0.16-0.71)**	**0.14 (0.04-0.41)**	**0.42 (0.21-0.83)**	**0.33 (0.13-0.82)**	0.92 (0.45-1.86)	0.87 (0.35-2.14)
Antimuscarinic drugs	0.81 (0.45-1.46)	0.99 (0.4-2.43)	1.29 (0.72-2.3)	0.75 (0.32-1.78)	1.24 (0.67-2.31)	0.88 (0.37-2.10)
Diuretics						
Surgeon volume						
Low	Reference	Reference	Reference	Reference	Reference	Reference
Medium	2.25 (0.86-5.88)	1.95 (0.57-6.58)	0.44 (0.17-1.1)	0.39 (0.15-1.04)	1.3 (0.49-3.46)	1.03 (0.3-3.58)
High	**2.59 (1.11-5.99)**	**4.51 (1.21-16.82)**	0.86 (0.39-1.9)	0.64 (0.17-2.25)	1.42 (0.61-3.33)	1.83 (0.48-6.94)
Department volume						
Low	Reference	Reference	Reference	Reference	Reference	Reference
High	0.84 (0.47-1.50)	0.96 (0.26-3.58)	1.01 (0.57-1.78)	1.5 (0.42-5.29)	0.82 (0.44-1.50)	0.72 (0.19-2.7)

Cure was dichotomized and throughout all analyses, adjusted by the preoperative ICIQ-SF- score ("severity").

Adjustment was made for age (continuous), BMI(continuous), ASA Classification (reference 1-2 (reference), yes), parity (continuous) previous hysterectomy (no (reference), yes), previous UI surgery (no (reference), yes), previous POP surgery (no (reference), yes), use of oestrogen preoperatively (no (reference), yes), use of antimuscarinic drugs (no (reference), yes) preoperatively, and use of diuretics preoperatively (no (reference), yes).

ICIQ-SF The International Consultation on Incontinence Questionnaire Short Form

BMI body mass index, *ASA* American Society of Anesthesiologist's Classification, *UI* Urinary incontinence, *POP* Pelvic organ prolapse.

Table 4 Uni -and multivariate analyses of potential predictors for hospital contact within 30 days

	Univariate analysis	Multivariate analysis
	Odds ratio (95%,CI)	Odds ratio (95%,CI)
Age, years, mean (SD)	**1.04 (1.02-1.06)**	**1.06 (1.03-1.09)**
BMI, kg/m^{2,}	0.98(0.94-1.02)	0.99 (0.97-1.01)
Type of UI		
Stress urinary	Reference	-
Urgency	0.82 (0.29-2.3)	
Mixed	1.01 (0.6-1.69)	
Not specified	1.32 (0.52-3.36)	
ASA		
1-2	Reference	
3-5	**1.63 (1.17-2.26)**	1.05 (0.64-1.72)
Parity	0.83 (0.68-1.02)	0.76 (0.57-1.01)
Previous surgery		
Previous hysterectomy	1.29 (0.79-2.1)	0.73 (0.36-1.48)
Previous UI surgery	1.35 (0.76-2.37)	0.9 (0.36-2.26)
Previous POP surgery	**3.18 (1.92-5.29)**	2.26 (0.95-5.34)
Use of preoperative medication		
Oestrogen	1.34 (0.87-2.06)	0.70 (0.34-1.43)
Antimuscarinic drugs	1.39 (0.90-2.16)	1.36 (0.7-2.66)
Diuretics	1.47 (0.99-2.18)	1.12(.58-2.17)
		-
Surgeon volume		
Low	Reference	Reference
Middle	0.66 (0.35-1.24)	0.45 (0.18-1.1)
High	0.64(0.39-1.05)	**0.35 (0.16-0.79)**
Department volume		
Low	Reference	Reference
High	0.71 (0.47-1.04)	**0.27 (0.09-0.76)**

BMI body mass index, *ASA* American Society of Anesthesiologist's Classification, *UI* Urinary incontinence, *POP* Pelvic organ prolapse.

Adjustment was made for age (continuous), BMI (continuous), ASA Classification (reference 1-2 (reference), yes), parity (continuous) previous hysterectomy (no (reference), yes), previous UI surgery (no (reference), yes), previous POP surgery (no (reference), yes), use of oestrogen preoperatively (no (reference), yes), use of antimuscarinic drugs (no (reference), yes) preoperatively, and use of diuretics preoperatively (no (reference), yes).

Comments

This national population-based cohort study on transurethral application of PAGH among 731 women, from 2007 through 2011, demonstrated that 29% of the women were cured while 9% had "no leakage at all" at three months follow up. There was a statistically significant improvement on the mean total ICIQ-SF score from 16 to 10.6.

The comparison with other studies on PAGH is hampered by the usage of different PROMs, definitions of cure, sample sizes, and follow-up periods [10,20,30].The short follow up of the present study differed from the ten PAGH studies which had follow up periods from one to three years [4-8,12,13]. Moreover, the majority of the studies reported results representing both one and more UITs [14]. The efficacy of PAGH is highest within three months [4,8,12] and hereafter the majority of women needs repeat surgery [31,32]. It is in this perspective that our results representing women with first-time UIT should be evaluated [8].

Overall, the efficacy of PAGH in the present study might seem in the lower end of the spectrum compared to the literature [4,6-13]. However, these results represented women with UIT in an everyday life setting and surgeons with different experience opposite to prospective studies financed by the industry where patients were "selected" [4,7,8,11] and surgeons who conducted the studies more likely were experienced surgeons from high volume departments[4,8]

Nevertheless, studies based exclusively on women with severe UI or previous surgical treatment for UI reported equivalent [5] or better results compared to ours [6,12,13]. The women in these studies might have benefitted from more repeat UITs. However, only one study reported cure after the second UIT and it was lower than compared to the first UIT [8].

The lower cure of UIT in the present study is more likely explained by the fact that the women in the study did not participate in a protocolled study and the results were obtained independently of the surgeon opposite to previous studies [4,6,8,13]. It is reasonable to assume that women tend to answer more positively when conscious of their participation in a clinical trial [33].

Finally, both definitions of "cure" and "no leakage at all" are fairly hard outcome measures. Synthetic MUSs and colposuspension, which are documented to be more effective [31], only demonstrate "no leakage at all" achieved in 40% and 30% of the patients at the long-term follow-up [34,35].

The right patient for UIT is still being disputed and predictors of lower cure among women are not well-understood [14,36]. There were among several patient characteristics only a few which were associated with lower cure.

The severity of UI preoperatively was consistently and independently associated with lower cure in all ICIQ-SF scores. There was no obvious influence of MUI and UUI on the cure and previous studies also only found borderline poorer outcome for women with MUI injected with PAGH [4,8,10]. However, women who used an antimuscarinic drug preoperatively had a decreased likelihood of cure, and this indicates that women with the most severe MUI and UUI might have a less chance of cure.

It seems paradoxical that the predictors for lower cure were found among women who most often have UIT – *i.e.* women with severe UI or severe MUI/UUI who are not suitable for the synthetic MUSs. This emphasizes the need for a proper patient counseling in order to provide women with realistic expectations regarding outcome.

Women treated by a high volume surgeon (>75 UITs) had significantly better outcomes on the frequency score and a significantly lower risk of hospital contacts within 30 days. Hitherto, only two studies have assessed that there seems to be a learning curve for UIT [4,16] and the present study also only indicated this.

Women treated at high volume departments had significantly lower risk of hospital contacts, which corresponds to a previous multicenter-study, which showed better results for departments that injected >15 UITs *per* year [4]. The influence of department volume in the present study probably reflects that there were significantly more performed by high volume surgeons at high volume departments compared to low volume departments.

The majority of departments (12 out of 16) rarely performed UIT. As the annual number of UITs has decreased to 200 UITs during recent years in Denmark [37], a surgeon volume of >75 UITs will be difficult to obtain in the future.

The study has several strengths. We reported outcomes based on a national population of women consecutively registered in the DugaBase. This represented everyday life as opposed to previous studies, which were either studies financed by the industry with several exclusion criteria [5,6,9,10] or studies on women with severe UI [6] and previous surgical treatment [4,7,8,11]. It is to the best of our knowledge the largest study on UIT with mainly PAGH. We reported on issues not addressed previously including several clinical confounders.

Outcome data were collected independently of the surgeon, which minimized the risk of investigator-bias. As outcome data on ICIQ-SF questionnaires and information on hospital contacts were obtained independently of exposure assessment, differential misclassification of the outcome was also minimized.

There were, however, also limitations of the study, as we were only able to examine PROMs at short-term follow up. Furthermore, this study only indicated a learning curve for UIT. Future studies including more PROMs (*e.g.* the PGI-I score) will perhaps support the evidence of a learning curve within UIT. Studies that explore aspects of this field are also needed, *e.g.* the threshold for acquiring the skill and which areas should be practiced.

Furthermore, we had no information on objective outcome measures such as surgical complications. There is at present focus on improving the database completeness for objective outcome measures making future studies within this field possible.

Due to the low database completeness of the DugaBase in the beginning of our study period [22], we cannot exclude some selection bias, as not all low volume departments were included in the study. Still, as all four high volume departments were registered in the DugaBase and did the majority of the UITs, the lack of a few low volume departments seems to be of minor importance as their contribution of UITs was small.

The lower data completeness could pose a selection bias, as some departments only follow-up on complicated patients. Sensitivity analyses, however, showed no differences with respect to department and surgeon volume between women who had filled in both questionnaires and women who had only completed pre- or postoperatively. Similarly, there were no differences in severity of UI preoperatively between women who had completed both questionnaires and women who had only filled in the questionnaire pre- or postoperatively. Last but not least, there were possible selection bias related to patient characteristics between women who had answered the questionnaires and women who had not completed the questionnaires. However, the little differences indicated that they were immaterial.

Conclusion

This national population-based cohort study represented women with a first-time injection at three months follow-up in an everyday life setting. The results might seem in the lower end of the spectrum in comparison to the literature.

However, cure of UIT should be seen in the perspective that is often performed in women who are not suitable for having or willing to have a synthetic MUS. A lower cure might therefore be acceptable as side effects are considerably fewer and milder compared to the synthetic MUSs.

The severity of UI preoperatively was a strong predictor of lower cure and similarly a use of antimuscarinic drug preoperatively which indicated a poorer outcome for women with severe MUI and UUI.A learning curve for UIT was found and that the treatment should be restricted to fewer hands to improve the surgical education and consequently cure for women with UIT.

Conflicts of interest:

Margrethe Foss Hansen had conference and travel expenses for the EUGA Leading Lights in Urogynaecology, Warszawa, paid by Astella. Gunnar Lose had consulting fee from Astella and Contura. None of the other authors received external funding for the study. The authors report no conflict of interest.

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Appendix Patient characteristics related to surgeon-and department volume, 2007-2011, Denmark

Variables	Surgeon volume				Department volume		
	0-25[1]	26-75[1]	> 75[1]	p-value [2]	0-15[3]	>15[3]	p-value [4]
Age, years, mean (SD)	66.5 (13.1)[5]	64.8 (13.9)[6]	63.5 (14.2)[7]	0.07	63.0 (15.0)[8]	65.4 (13.2)[9]	**0.02**
BMI, mean (SD)	28.2 (6.4)[10]	27.2 (5.6)[11]	26.3 (4.9)[12]	**0.002**	28 (6.4)[13]	26.2 (4.7)[14]	**0.001**
Type of UI							
Stress	33/85(38.8)	24/101(23.7)	103/323(31.9)	0.3	54/170(31.8)	115/375(30.7)	0.52
Urgency	5/85 (5.8)	9/101 (8.9)	17/323 (5.2)		9/170 (5.3)	29//375 (7.7)	
Mixed	43/85 (50.6)	64/ 101 (63.4)	183/ 323 (56.7)		99/170 (58.2)	205/375 (54.7)	
Not specified	4/85 (4.7)	4/ 101 (3.9)	20/323 (6.2)		8/170 (4.7)	26/375 (6.9)	
Smoking	18/74 (24.3)	17/91 (18.7)	61/317 (19.2)	0.58	36/156 (23.1)	64/349 (18.3)	0.22
Alcohol units per week, mean(SD)	2.3 (4.0)[15]	2.8 (4.5)[16]	2.7 (4.3)[17]	0.78	2.7 (4.3)[18]	2.8 (4.4)[19]	0.71
ASA							
1-2	64/ 86 (74.4)	82/98 (83.7)	272/301 (90.3)	**0.001**	138/172 (80.2)	289/324 (89.2)	**0.006**
3-5	22/86 (25.6)	16/98 (16.3)	29/301 (9.6)		34/172 (19.8)	35/324 (10.8)	
Parity, mean (SD)	2.3 (1.2)[20]	2.2 (1.3)[21]	2.3 (1.2)[22]	0.31	2.1 (1.2)[23]	2.3 (1.2)[24]	**0.03**
Previous surgery							
Hysterectomy	34/91 (37.4)	29/107 (27.1)	104/330 (31.5)	0.30	57/179 (31.8)	123/380 (32.4)	0.90
UI surgery	17/92 (18.5)	19/108 (17.6)	60/326 (18.4)	0.98	28/180 (15.6)	73/378 (19.3)	0.28
POP surgery	15/90 (16.7)	20/105 (19.0)	64/326 (19.6)	0.82	34/177 (19.2)	72/377 (19.1)	0.98
Use of preoperative medication							
Oestrogen	84/119(70.6)	92/133 (69.2)	268/439 (61)	**0.02**	159/258(61.6)	324/491 (65.9)	0.23
Ant muscarinic drugs	84/ 119(70.6)	38/133(28.5)	109/439 (24.8)	0.46	63/258 (24.4)	125/491 (25.5)	0.76
Diuretics	62/119 (52.1)	56/ 133(42.1)	174/439 (39.6)	**0.02**	114/258 (44.2)	204/491 (41.6)	0.49
Other drugs	4/119 (3.4)	5/133 (3.8)	27/439 (6.2)	0.25	9/258 (3.5)	32/491 (6.5)	0.08

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The extent of the candidate's contribution to the article is assessed on the following scale

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C. did the majority of the work (67-100%)

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3. Involvement in the analysis or the concrete experiments/investigation.	B
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3.	Involvement in the analysis or the concrete experiments/investigation.	B
4.	Presentation, interpretation and discussion of the results obtained in the form of an article or manuscript.	C

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