# Surgical treatment for urinary incontinence in women - Danish nationwide cohort studies

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### The 3 original papers are

## 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].

Ill: 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 41<sup>st</sup> 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)

### 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 Health and Medicines 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

### 1. INTRODUCTION

### 1. BACKGROUND

Urinary incontinence (UI) is defined as the complaint of involuntarily loss of urine (2). Although not life threatening, this condition can have physical, psychological and social consequences for the individual (3, 4). 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 (5). Among a Danish cohort of women aged 40-60 years, the prevalence of one involuntarily leakage per week has been estimated as 16% (6). 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+ (7) and better treatment modalities (5). The most frequent type of UI is stress urinary incontinence (SUI)(50%), followed by mixed UI (MUI)(36%) and pure urgency UI (UUI)(11%) (8). 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 (9). 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 (5).

### 2. SURGICAL TREATMENT FOR URINARY INCONTINENCE

The current standard surgical intervention is the synthetic midurethral sling (MUS) (10), which is a tape made of polypropylene placed mid-urethra under tension (5).

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 (11).

The tension-free vaginal tape (TVT) was the first synthetic MUS and has shown objective and subjective cure rates of 85% (12, 13). 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 (10). The efficacy is similar for both synthetic MUSs at short and mid-term follow-ups (14-17). Several modifications of the synthetic MUSs have subsequently been introduced, but without clinical data on their safety and efficacy (5). Urethral injection therapy (UIT) is less minimal invasive than the synthetic MUSs and adverse events are fewer and more mild and moderate (18, 19), but as the efficacy is lower (18, 19) it is often used as a second line approach (10).

## 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 (20, 21). Influence of these factors on the surgical treatment for UI have previously been investigated in Danish studies (22-25) 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) (26). The association between department and surgeon volume and quality of care has generally been demonstrated as being positive or neutral, and never negative (27). The most complex procedures tend to have the strongest volume-outcome association (26). Although both department volume and surgeon volume are assumed to affect the outcome, their relative contributions have not been established (26). Crucial for the understanding of the volume-outcome relationship is that there is not a priori a positive correlation between department and surgeon volume (21). 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 (20). 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 (21, 27).

# 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 (28-30), but also in terms of lowering the risk of complications (31) and achieving better subjective outcomes (23, 32). 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 (33). 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 (22-25, 34, 35).

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) (34, 35). Many different procedures *per* department were in usage in 2001, but were reduced by the end of 2009 (34, 35).

However, a substantial variation in the assessment and surgical treatment for UI at the respective departments persisted (35) despite the fact that national guidelines for the treatment of UI had been put in place (35).

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 (23-25). Partly in recognition of this, the Danish Health and Medicines Authority (DHMA) introduced requirements for department volume (36) and in the year 2010 further centralization within the specialty of Gynaecology was established (37).

2001	2002	2003	2004	2005	2005	2007	2008	2009	2010	
Gynaecology, Urology Gastro-intestinal surgery*	Guidelines Danish Society of Obstetrics and Gymaecology			Establishment: The Danish Society of <u>Urogynaecology</u>	Establishment: The Danish <u>Urogymaecological</u> Database	The Danish Health and Medicines Authorities: Requirement of centralization at fewer departments		<u>Gynaecology</u> <sup>6</sup>		

## 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.

**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) (32, 38-41). 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 (32, 38, 39, 41), but have now become more established as financed by the government (32, 38, 39, 41). The DugaBase, however, is the only database that it is mandatory by law to report to (41) (*Personal comment: Rune Svenningsen, Steven Schraffordt, Jonathan Duckett, Thomas Aigmueller*).

The Danish Urogynaecological Database (DugaBase) was established in 2006 (41). 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 patientrelated data and objective and subjective outcomes based on a national population (41-44).

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.

### 5. REOPERATION FOR URINARY INCONTINENCE

The risk of reoperation after surgical treatment for UI based on national populations has not been established internationally (11, 45, 46). Existing literature specifies an overall lifetime rate of reoperation of about 8-9% after an initial operation for UI (11). 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 longterm follow-up (5 -10 years) (13, 47, 48). 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.

### 6. 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 (49, 50). There is, however, no consensus on which treatment should be used (49, 51, 52). The literature indicates that synthetic MUSs represent the leading treatment option for repeat surgery, but the results are limited to short-term follow-up (53). A variety of surgical treatments exists, but there is little data to support their use (49, 53). 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 (49).

# 7. URETHRAL INJECTION THERAPY FOR STRESS AND MIXED URINARY INCONTINENCE

UIT has been performed since the early 20<sup>th</sup> century (54) and a variety of agents have been launched, but several of these

were retracted due to product related side effects (19). It is an attractive alternative to synthetic MUSs due to its few and mild side effects (55). Polyacrylamide hydrogel (PAGH) was introduced in Europe as a bulking agent in 2006 and is now widely used (56, 57). The current knowledge on PAGH is based on ten studies with a follow-up period of one to three years (22, 58-66). However, no national population-based studies of PAGH have been conducted and there is a lack of studies representing patients in the daily clinic (57). **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:

-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). -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). -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 fiveyear period (2007-2011) and the influence of department volume, surgeon volume and patient-related factors (Study III).

### 2. MATERIALS AND METHODS

### 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 (67, 68). Denmark has approximately 5.5 million inhabitants and consists of five regions.

### SOURCE OF DATA

All Danish residents are assigned a unique Civil Registration Number (CPR-number), which enables linkage between all nationwide registries (69). 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 (69).

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 (67, 68). 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 (70). 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 (41, 42). It is mandatory by law for all hospital departments and private hospitals to report to the DugaBase (41).

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 (1, 41), 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 (43). The ICIQ-SF has been translated into, but not validated in, Danish (42) 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 (1, 41). The database completeness has remained as high as 92.6 % for surgical treatment for UI in 2014 (71). During the years 2007-2011 the data completeness has constantly been lower and was in 2014 52.7% (71). 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 (41). 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 (41).

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 (72). Only a few studies have therefore assessed the completeness and validity of this register (73, 74). There are, however, factors which point towards a high data quality (72). 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 (72). 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 (72).

### 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 (75). 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.

### Figure 2 Derivation of study cohort (Study 1)



### 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).

### **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 (76).

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 (1, 22, 58-61, 65). 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 (1) and on "no leakage at all " defined on the frequency score as answering never to leakage of urine (58). "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 (77).

Department volume was defined as in a previous study, high (≥15 UITs *per* year) and low (<15 *per* year) (22). 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 CO3) 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)



### 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  $\chi^2$ -test and the  $\chi^2$ -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  $\chi^2$ -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  $\chi^2$ -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  $\chi^2$ -test for trend (categorical variables) and one way analysis of variance (ANOVA) (continuous variables) and for department volume the  $\chi^2$ -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.

### 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

(<u>http://www.dnvk.dk/CVK/Home/English.aspx</u>) as they were register-based studies.

### 4. MAIN RESULTS

### STUDY I

A total of 8671 women (56.1 years,  $\pm$  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	Medium	High	Total	Low	Medium	High	Total
	(n = 221)	(n = 519)	(n = 1820)	(n = 2560)	(n= 424)	(n = 1576)	(n = 4111)	(n = 6111)
TVT (%)	56 (25)	102 (20)	73(40)	889 (35)	289 (68)	1178 (75)	2674 (65)	414 (68)
TOT (%)		1	-	1	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%; Cl), Reoperation	Adjusted Hazard ratio (95%; Cl), reoperation •
TVT	(Reference)	(Reference)
тот	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

<sup>a</sup> Adjusted for age, department volume, and calendar effect (1998-2002, 2003-2007).

#### Study II

From 1998 to 2007, 5820 women (mean age 55.4  $\pm$  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 *
Low volume Department (%)	467 (100)	445 (95.3)	22 (4.7)	0.23 <sup>b</sup>
Medium volume Department (%)	1429 (100)	1343 (94.0)	86 (6.0)	
High volume Department (%)	3924 (100)	3678 (93.7)	246 (6.3)	

<sup>a</sup> Student's t-test

 ${}^{\scriptscriptstyle b}\chi^2\text{-}$  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).

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

	Complete cohort	No reoperation	Reoperation	P value
Ν	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 •
Low volume Department (%)	345 (100)	336 (97.4)	9 (2.6)	0.098 *
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

<sup>a</sup> Student´s t-test

 ${}^{b}\chi^{2}$ - 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 •	
Low volume Department (%)	122 (100)	109 (89.3)	13 (10.7)	0.91 <sup>b</sup>	
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

<sup>a</sup> Student's t-test

 ${}^{b}\chi^{2}$ -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									Pe	riod 2003-200	7		
Baseline	TVT	UIT	Colgo- 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. <u>2</u> )	15 (6.3)	94 (39.3)	2 (0.84)	4 (1.7)	35 (14.6)	239 (100)
TOT (%)*		-			-		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)	45 (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

<sup>a</sup> 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	тот	UIT	Colposuspension	<u>Puboxaginal</u> 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

### 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*	
Age, years, mean (SD)	64.0 (13.9)	_
BMI, mean (SD)	26.7 (5.3) <sup>2</sup>	
Type of UI		
Stress	152/490 (31.0)	
Urgency	35/490 (7.1)	
Mixed	277/490 (56.5)	
Not specified	26/490 (5.3)	
ŝmoking	100/505 (19.8)	
Alcohol units per week, mean (SD)	2.8 (4.4) *	-
ASA		_
1-2	394/458 (86.0)	
3-5	64/458 (14.0)	
Parity, mean (SD)	2.3 (1.2)*	_
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.

# 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% Cl 0.09-0.76).

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

Variables	Fr	equency		Amount		Impact
	univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
	Odds ratio (95%, CI)	Odds ratio (95%, CI)	Odds ratio (93%, CI)	Odds ratio (95%, CI)	Odds ratio (95%, CI)	Odds ratio (95%, CI)
ige, years	0.95 (0.95-1.00)	0.99 (0.95-1.03)	0.95(0.95-1.00)	0.95(0.95-1.01)	1.01 (0.95-1.03)	1.02 (0.95-1.05)
MI, kg/m*	0.95 (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)
rype of UI Stress Urgency Nitised Not specified	Reference 0.42 (0.12-1.46) 1.19 (0.63-2.24) 2.82 (0.70-11.22)		Reference 0.65 (0.22-1.93) 0.96 (0.52-1.78) 0.55 (0.14-2.12)		Reference 1.15 (0.37-3.55) 1.76 (0.88-3.48) 0.77 (0.19-3.12)	
1-2 3-5	Reference 0.53 (0.33-0.84)	Reference 0.67 (0.34-1.3)	Reference 0.67 (0.43-1.05)	Reference 0.81 (0.43-1.51)	Reference 0.80 (0.50-1.28)	Reference 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 UI surgery POP surgery	1.15(0.65-2.12) 1.21(0.59-2.46) 1.07(0.51-2.26)	1.12 (0.45-2.59) 1.52 (0.56-5.93) 0.39 (0.10-1.54)	1.72 (0.92-3.21) 0.99 (0.45-2.14) 1.47 (0.65-3.34)	1.44 (0.59-3.45) 0.62 (0.18-2.09) 5.62 (1.25-25.32)	1.09 (0.57-2.07) 0.68 (0.30-1.51) 0.84 (0.34-2.04)	0.64 (0.27-1.54) 1.18 (0.37-5.74) 0.80 (0.21-2.95)
Preoperative medication Oestrogen Antimuscacioic drugs Divretics	0.62 (0.34-1.14) 0.34 (0.16-0.71) 0.81 (0.45-1.46)	0.62 (0.25-1.57) 0.14 (0.04-0.41) 0.99 (0.4-2.43)	0.55 (0.29-1.00) 0.42 (0.21-0.83) 1.29 (0.72-2.3)	0.56 (0.22-1.40) 0.33 (0.13-0.82) 0.75 (0.32-1.78)	0.78 (0.41-1.49) 0.92 (0.45-1.86) 1.24 (0.67-2.31)	1.12 (0.46-2.7) 0.87 (0.35-2.14) 0.88 (0.37-2.10)
lurgeon volume Low Medium High	Reference 2.25 (0.86-5.88) 2.59 (1.11-5.99)	Reference 1.95 (0.57-6.58) 4.51 (1.21-16-82)	Reference 0.44 (0.17-1.1) 0.86 (0.39-1.9)	Reference 0.39 (0.15-1.04) 0.64 (0.17-2.25)	Reference 1.3 (0.49-3.46) 1.42 (0.61-3.33)	Reference 1.03 (0.3-3.58) 1.83 (0.48-6.94)
Department volume Low High	Reference 0.84 (0.47-1.50)	Reference 0.96 (0.26-3.58)	Reference 1.01 (0.57-1.78)	Reference 1.5 (0.42-5.29)	Deference 0.82 (0.44-1.50)	Reference 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**

### **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 fiveyear period (Study I). An Austrian single centre study (n=101) showed a similar rate of reoperation after TVT of 6% after five years (13) 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 (47, 48). 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) (11, 45) and 3.76% at seven years follow- up (synthetic MUSs) (45).

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 (78-80).

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 (44). 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 (81).

Financial incentives such as reimbursement can also influence the incidence of surgery for both patients and healthcare providers (79). Because Denmark, unlike the USA and Taiwan for example (11, 67, 82), 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 (83, 84) and is easy and inexpensive to identify (85). There are however disadvantages to using it comparatively across hospital departments (85, 86). 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 (83, 84). Secondly, the risk of confounding is higher if information is based exclusively on administrative data or clinical data not adjusted for patient-related factors (79). Thirdly, as the number of reoperations after synthetic MUS is generally low (49, 87) and even lower at the respective departments (88), this will impede the statistical precision (20, 88). 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 (14-16) and a Cochrane-study (2009) (17) 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 (10, 89-92). 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) (10, 93, 94) and the recently updated Cochrane (2015) (published after Study I) supplemented by longer follow-up periods also support the contention of our observations (95). 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 longterm follow-up ≥ 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) (95).

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) (96). A low *maximum urethral closure pressure* (MUP) is associated to severe UI (10, 97-99) and the MUP has proved

to decrease significantly with increasing age, after the woman has passed the age of 25 years (100). Therefore, it also seems reasonable that women with a low MUP are documented to have significantly less success with TOT than with TVT (10, 97-99).

Anatomically there are differences between TVT and TOT in compression of the urethra, which might explain the differences in effectiveness and durability (99). Both slings rely on the hammock hypothesis and the integral theory (101-103), where continence is achieved, by placing a vaginal tape underneath the mid-urethra. The TVT thus reinforces the weakened pubovaginal ligaments without tension (103). 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 (98). 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 (98).

### 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).



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### 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 (49). In this nationwide population-based study of 820 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 (51, 82).

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 (10). It was however more frequently used (42%), compared with the UK (14%) and Taiwan (11%) (51, 82) 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 (51) and this probably reflects the fact that both procedures are rarely used as primary surgery for UI (51). 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 (82).

# 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 (22, 58-66), of which four were largescale studies (n= 135-256) (22, 61, 64, 65) and the remaining small-scale studies (n = 20-82) (58-60, 62, 63, 66) (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 (22, 58-60, 62, 63, 65). The efficacy of PAGH is highest at three months (22, 61, 64, 65) after which the majority of women need repeat surgery (18, 19). 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 (22, 59-66). Prospective studies, of which two were large multicentre studies (22, 61) had extremely strict inclusion criteria. For example, none of the studies included women with prior surgical treatment for UI (22, 60, 61, 64) and one study excluded women with MUI (60). 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 (22, 61, 64). Studies based exclusively on women with severe UI or previous surgical treatment for UI reported equivalent (64) or slightly better results compared to ours (59, 65, 66).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 (61).

# Table 10 Studies on urethral injection therapy withpolyacrylamide hydrogel

first author , date	Type of study	See	follow-	Ast	Subjective evidence	icio er total Presentively	icic-ar total Factoreratively	2	Delusion- critoria	Noting
Lose, 2010 (22)	Prospective multicentre Observational	135	12 menths	56 (29-62)	1010-5* VAS	18	,	4 0.001	Previews Clisurgey, UT, Mediadan for Cl	Induates
Zudoqiaku. 2011 (62)	Prespective Observational	84	9 mantha	69 (41-87)	100					Nece
Tesur Hebson, 2012 (61)	Prespective multisente Obsorvational		24 months		1010-5* VAS	18	,	4 0.005	Previews Ul surgery, UlT, Medication for Ul	Industry
Maggiora, 2013 (60)	Prespective Observational	82	12 months	54.3 (s7.0)	20-3 20-1 10-7	14.2	••	¥ 0.001	Provious Ul surgery, POP Surgery, OAE, MUI, POP 52	Induatey
60904 2014 (89)	Prespective Observational	=0	18.6 mantha	72.8 (412)	10.0.5P Fair	17		× 10 <sup>-1</sup>		Nene
64x64x6. 2014 (5.8)	Refrespective abservational	82	22 marths	70 (18-90)	1010-5* VAS	17.6	10.6	4 0.001		Nece
Bekej, 2014 (84)	Single blind Rendemized Controlled Trial	229 12. 110	12 months	55.5 (23.3- 98.4) 56.7 (22.3- 65.4)	1010 1100 410 710	-	-		-	industry
2014, Verbisli- Soldause (63)	Prespective observational	20	24 months	84.5 (80-87)	001 107 207 245	-	-		-	Nens
2018	Prespective		as months	10.0 (51-95)			-	* 0.001		Nene
2016, Doesnoo (66)	Prespective observational	••	12 mantha	71.7 (10.7)	VAS			-	MUI, tapo Insector Soundly outside the outworks Leone, Obstructive tapo Insector or post void residual (vetures >soom).	Nens
Menalon MP	Actrospective		3	64.0			100	**		None

 $\operatorname{ICIQ}\operatorname{-SF}$  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

### 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 (11). Whether or not the department volume influences the risk of reoperation after synthetic MUSs remains controversial as one populationbased cohort study found no difference (45) and two other population-based cohort studies found an increased risk of reoperation after TVT and synthetic MUSs at low volume departments (82, 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 (35, 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 (97, 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 (20, 21), 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 (22). 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 (22, 110). The learning curve for UIT would appear to be high (>75 UITs) compared to TVT which has a learning curve of 20 procedures (28-31). One possible explanation is that UIT is a technically complicated procedure (22) 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 (21, 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 (22, 61, 63).

The right patient for UIT is still being disputed and predictors of lower success among women are not well understood (57, 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 (21). 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.

### 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 (67-69) . 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 (70). 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 (41).

### 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.

### 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.

### 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.

### 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 (99).Women with MUI seems to benefit from receiving a TOT (98, 114) whereas women with severe UI (*i.e.* sphincter deficiency) have more success with TVT (10, 97, 99). 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.

### **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 (21). As only a few studies have explored aspects of department volume within the surgical treatment for UI (22-25, 45, 81, 82) 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 (45, 81). 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 (44).

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 (22).

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 NOMESCOprocedure 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 (11, 82) except for one study, which excluded UIT at baseline and at reoperation (45).

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.

### 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.

### 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 noncausal associations (Fig.7) emphasizing the importance of many other factors than statistical significance testing (117).

We evaluated various exposures and we believe patientrelated 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:

### 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.

### **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.

### 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

### 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.

# 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.

### **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:

- 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).
- 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).
- 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% Cl, 1.5 -2.9) compared with TVT.

<u>Study II</u>: 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 followup. 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 followup 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 ( $\leq$  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

<u>Study I</u>: 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.

### 9. References

1. Database DU. Danish Urogynaecological Database, annual report 2007 2007 [12.08.2016].

2. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Subcommittee of the International Continence Society. American journal of obstetrics and gynecology. 2002/07/13 ed2002. p. 116-26.

3. Riss P, Kargl J. Quality of life and urinary incontinence in women. Maturitas. 2011;68(2):137-42.

4. Pakgohar M, Sabetghadam S, Vasegh Rahimparvar SF, Kazemnejad A. Quality of life (QoL) and help-seeking in postmenopausal women with urinary incontinence (UI): A population based study. Arch Gerontol Geriatr. 2014;59(2):403-7.

5. Norton P, Brubaker L. Urinary incontinence in women. Lancet. 2006;367(9504):57-67.

6. Moller LA, Lose G, Jorgensen T. The prevalence and bothersomeness of lower urinary tract symptoms in women 40-60 years of age. Acta obstetricia et gynecologica Scandinavica. 2000;79(4):298-305.

7. Giannakouris K. Ageing characterises the demographic perspectives of the European societies Eurostat statistics in focus 72/2008 [cited 2016 12.8.2016]. Available from: http://www.apapr.ro/images/BIBLIOTECA/demografie/eurostat%20focus%202008.pdf.

8. Hannestad YS, Rortveit G, Sandvik H, Hunskaar S. A community-based epidemiological survey of female urinary incontinence: the Norwegian EPINCONT study. Epidemiology of Incontinence in the County of Nord-Trondelag. Journal of clinical epidemiology. 2000;53(11):1150-7.

9. Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. International urogynecology journal. 2010;21(1):5-26. 10. Schierlitz L, Dwyer PL, Rosamilia A, Murray C, Thomas E, De Souza A, et al. Effectiveness of tension-free vaginal tape compared with transobturator tape in women with stress urinary incontinence and intrinsic sphincter deficiency: a randomized controlled trial. Obstetrics and gynecology. 2008;112(6):1253-61.

 Jonsson Funk M, Siddiqui NY, Kawasaki A, Wu JM. Longterm outcomes after stress urinary incontinence surgery. Obstetrics and gynecology. 2012;120(1):83-90.
 Ward KL, Hilton P. Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up. BJOG : an international journal of obstetrics and gynaecology. 2008;115(2):226-33.
 Bjelic-Radisic V, Greimel E, Trutnovsky G, Zeck W, Aigmueller T, Tamussino K. Patient-reported outcomes and urinary continence five years after the tension-free vaginal tape operation. Neurourology and urodynamics. 2011;30(8):1512-7.

14. Novara G, Ficarra V, Boscolo-Berto R, Secco S, Cavalleri S, Artibani W. Tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials of effectiveness. European urology. 2007;52(3):663-78. 15. Latthe PM, Foon R, Toozs-Hobson P. Transobturator and retropubic tape procedures in stress urinary incontinence: a systematic review and meta-analysis of effectiveness and complications. BJOG : an international journal of obstetrics and gynaecology. 2007;114(5):522-31.

16. Novara G, Artibani W, Barber MD, Chapple CR, Costantini E, Ficarra V, et al. Updated systematic review and metaanalysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence. European urology. 2010;58(2):218-38.

17. Ogah J, Cody JD, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane database of systematic reviews (Online). 2009(4):Cd006375.

18. Kirchin V, Page T, Keegan PE, Atiemo K, Cody JD, McClinton S. Urethral injection therapy for urinary incontinence in women. Cochrane database of systematic reviews (Online). 2012;2:Cd003881.

 Mohr S, Siegenthaler M, Mueller MD, Kuhn A. Bulking agents: an analysis of 500 cases and review of the literature. International urogynecology journal. 2013;24(2):241-7.
 Christian CK, Gustafson ML, Betensky RA, Daley J, Zinner MJ. The volume-outcome relationship: don't believe everything you see. World J Surg. 2005;29(10):1241-4.

21.Chowdhury MM, Dagash H, Pierro A. A systematic review of the impact of volume of surgery and specialization on patient outcome. Br J Surg. 2007;94(2):145-61.

22. Lose G, Sorensen HC, Axelsen SM, Falconer C, Lobodasch K, Safwat T. An open multicenter study of polyacrylamide hydrogel (Bulkamid(R)) for female stress and mixed urinary incontinence. International urogynecology journal. 2010;21(12):1471-7.

23. Ammendrup AC, Jorgensen A, Sander P, Ottesen B, Lose G. A Danish national survey of women operated with midurethral slings in 2001. Acta obstetricia et gynecologica Scandinavica. 2009;88(11):1227-33.

24. Ammendrup AC, Bendixen A, Sander P, Ottesen BS, Lose G. [Urinary incontinence surgery in Denmark 2001-2003]. Ugeskrift for laeger. 2009;171(6):399-404.

25. Ammendrup AC, Sorensen HC, Sander P, Lose G. [Surgical treatment of female urinary incontinence]. Ugeskr Laeger. 2010;172(6):456-60.

26. Kraus TW, Buchler MW, Herfarth C. Relationships between volume, efficiency, and quality in surgery--a delicate balance from managerial perspectives. World J Surg. 2005;29(10):1234-40.

27. Mainz J, Bartels P, Bek T. Hvordan kan man sikre kvaliteten af sundhedsvæsenets ydelser- struktur og organisation. Kvalitetsudvikling i praksis. 1: Munksgaard; 2011. p. 73-87.

Neuman M. TVT and TVT-Obturator: comparison of two operative procedures. European journal of obstetrics, gynecology, and reproductive biology. 2007;131(1):89-92.
 Groutz A, Gordon D, Wolman I, Jaffa AJ, David MP, Lessing JB. Tension-free vaginal tape for stress urinary incontinence: Is there a learning curve? Neurourology and urodynamics. 2002;21(5):470-2.

 Hilton P, Rose K. The "learning curve" for retropubic midurethral sling procedures: a retrospective cohort study.
 International urogynecology journal. 2016;27(4):565-70.
 Welk B, Al-Hothi H, Winick-Ng J. Removal or Revision of Vaginal Mesh Used for the Treatment of Stress Urinary Incontinence. JAMA Surg. 2015;150(12):1167-75.
 Schraffordt Koops SE, Bisseling TM, Heintz AP, Vervest HA. Prospective analysis of complications of tension-free vaginal tape from The Netherlands Tension-free Vaginal Tape study. American journal of obstetrics and gynecology. 2005;193(1):45-52.

33. Mainz J, Bartels P, Bek T. Hvad er kvalitet og kvalitetsudvikling? Kvalitetsudvikling i praksis. 1: Munksgaard; 2011. p. 19-33.

34. Health Care Consulting, Center for Evaluering og Medicinsk T. Inkontinensbehandling i Danmark : en statusbeskrivelse over ambulant behandling af patienter med urininkontinens på landets sygehuse. Kbh.: Center for Evaluering og Medicinsk Teknologivurdering; 2001. Available from:

### http://sundhedsstyrelsen.dk/~/media/D92DFEA0C75A4AB3 8DEC2A1C308E09A1.ashx.

35. Health Care Consulting, Center for Evaluering og Medicinsk T. Urininkontinens hos kvinder : evaluering af udredning og behandling i almen praksis og på hospital: Sundhedsstyrelsen; 2009. Available from:

http://www.sst.dk/publ/publ2010/EMM/Urininkontinens/Ev aluering\_urininkontinens.pdf.

36. Danish Health and Medicines Authorities. Rapport for specialet: Gynækologi og Obstetrik 2007.

http://sundhedsstyrelsen.dk/~/media/05C4BA5236744D40B 7D12A6566D80BD2.ashx.

37. Hansen MF, Lose G, Kesmodel US, Gradel KO. Forandringer inden for den kirurgiske behandling af urininkontinens. DUGSNyt2; 2013.

38. Kulseng-Hanssen S. The development of a national database of the results of surgery for urinary incontinence in women. BJOG : an international journal of obstetrics and gynaecology. 2003;110(11):975-82.

39. Elbiss HM, Thomson AJ, Moran PA. How useful are the BSUG database outcome criteria: validation using the MESA questionnaire. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology. 2010;30(7):716-40. Tamussino K, Hanzal E, Kolle D, Ralph G, Riss P. The Austrian tension-free vaginal tape registry. International urogynecology journal and pelvic floor dysfunction. 2001;12 Suppl 2:S28-9. 41. Guldberg R, Brostrom S, Hansen JK, Kaerlev L, Gradel KO, Norgard BM, et al. The Danish Urogynaecological Database: establishment, completeness and validity. International urogynecology journal. 2012;6(24):983-90.
42. Guldberg R, Kesmodel US, Hansen JK, Gradel KO, Brostrom S, Kaerlev L, et al. Patient reported outcome measures in women undergoing surgery for urinary incontinence and pelvic organ prolapse in Denmark, 2006-2011. International urogynecology journal. 2013;24(7):1127-34.

43. Larsen MD, Lose G, Guldberg R, Gradel KO. Discrepancies between patient-reported outcome measures when assessing urinary incontinence or pelvic- prolapse surgery. International urogynecology journal. 2015;4(27):537-43.
44. Maher CM, Feiner B, Baessler K, Glazener CM. Surgical management of pelvic organ prolapse in women: the updated summary version Cochrane review. International urogynecology journal. 2011;22(11):1445-57.
45. Fialkow M, Symons RG, Flum D. Reoperation for urinary

incontinence. American journal of obstetrics and gynecology. 2008;199(5):546 e1-8.

46. Abdel-Fattah M, Familusi A, Fielding S, Ford J, Bhattacharya S. Primary and repeat surgical treatment for female pelvic organ prolapse and incontinence in parous women in the UK: a register linkage study. BMJ open. 2011;1(2):e000206.

47.Aigmueller T, Trutnovsky G, Tamussino K, Kargl J, Wittmann A, Surtov M, et al. Ten-year follow-up after the tension-free vaginal tape procedure. American journal of obstetrics and gynecology. 2011;205(5):496.e1-5.

48. Svenningsen R, Staff AC, Schiotz HA, Western K, Kulseng-Hanssen S. Long-term follow-up of the retropubic tensionfree vaginal tape procedure. International urogynecology journal. 2013;24(8):1271-8.

49. Bakali E, Buckley BS, Hilton P, Tincello DG. Treatment of recurrent stress urinary incontinence after failed minimally invasive synthetic suburethral tape surgery in women. Cochrane database of systematic reviews (Online). 2013;2:CD009407.

50. Smith AR, Artibani W, Drake MJ. Managing unsatisfactory outcome after mid-urethral tape insertion. Neurourology and urodynamics. 2011;30(5):771-4.
51. Patil A, Moran P, Duckett J. How do urogynaecologists treat failed suburethral slings? Experience from the British Society of Urogynaecology database and literature review. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology. 2011;31(6):514-7.
52. Hashim H, Terry TR. Management of recurrent stress urinary incontinence and urinary retention following midurethral sling insertion in women. Ann R Coll Surg Engl. 2012;94(7):517-22.

53. Nadeau G, Herschorn S. Management of recurrent stress incontinence following a sling. Current urology reports. 2014;15(8):427.

54. Meyer L. 2 tilfælde af incontinentia urinae helbredte ved parafininjektioner. Ugeskrift for Læger. 1904;104:5.
55. Kotb AF, Campeau L, Corcos J. Urethral bulking agents: techniques and outcomes. Current urology reports. 2009;10(5):396-400.

56. Lose G, Mouritsen L, Nielsen JB. A new bulking agent (polyacrylamide hydrogel) for treating stress urinary incontinence in women. BJU international. 2006;98(1):100-4.
57. Kasi AD, Pergialiotis V, Perrea DN, Khunda A, Doumouchtsis SK. Polyacrylamide hydrogel (Bulkamid(R)) for stress urinary incontinence in women: a systematic review of the literature. International urogynecology journal. 2016;27(3):367-75.

58. Martan A, Masata J, Svabik K, El-Haddad R, Hubka P. [Transurethral injection of polyacrylamide hydrogel (Bulkamid(R)) for the treatment of female stress urinary incontinence and changes in the cure rate over time]. Ceska gynekologie / Ceska lekarska spolecnost J Ev Purkyne. 2013;78(6):554-9.

59. Beraru A, Droupy S, Wagner L, Soustelle L, Muyschondt C, Ben Naoum K, et al. [Efficacy of periurethral injections of polyacrylamide hydrogel (Bulkamid((R))) and quality of life of patients with urinary incontinence due to sphincter deficiency (IUE-IS)]. Progres en urologie : journal de l'Association francaise d'urologie et de la Societe francaise d'urologie. 2014;24(8):501-10.

60. Leone Roberti Maggiore U, Alessandri F, Medica M, Gabelli M, Venturini PL, Ferrero S. Outpatient periurethral injections of polyacrylamide hydrogel for the treatment of female stress urinary incontinence: effectiveness and safety. Archives of gynecology and obstetrics. 2013;288(1):131-7. 61. Toozs-Hobson P, Al-Singary W, Fynes M, Tegerstedt G, Lose G. Two-year follow-up of an open-label multicenter study of polyacrylamide hydrogel (Bulkamid(R)) for female stress and stress-predominant mixed incontinence. International urogynecology journal. 2012;23(10):1373-8. 62. Trutnovsky G, Tamussino K, Greimel E, Bjelic-Radisic V. Quality of life after periurethral injection with polyacrylamide hydrogel for stress urinary incontinence. International urogynecology journal. 2011;22(3):353-6. 63. Vecchioli-Scaldazza CV, Smaali C, Morosetti C, Azizi B, Giannubilo W, Ferrara V. Polyacrylamide hydrogel (bulkamid(R)) in female patients of 80 or more years with urinary incontinence. International braz j urol : official journal of the Brazilian Society of Urology. 2014;40(1):37-43. 64. Sokol ER, Karram MM, Dmochowski R. Efficacy and safety of polyacrylamide hydrogel for the treatment of female stress incontinence: a randomized, prospective, multicenter North American study. The Journal of urology. 2014;192(3):843-9.

65. Pai A, Al-Singary W. Durability, safety and efficacy of polyacrylamide hydrogel (Bulkamid((R))) in the management of stress and mixed urinary incontinence: three year follow up outcomes. Cent European J Urol. 2015;68(4):428-33.
66. Zivanovic I, Rautenberg O, Lobodasch K, von Bunau G, Walser C, Viereck V. Urethral bulking for recurrent stress urinary incontinence after midurethral sling failure. Neurourology and urodynamics. 2016.

67. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-90.

 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scandinavian journal of public health. 2011;39(7 Suppl):30-3.

69. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. European journal of epidemiology. 2014;29(8):541-9.

70. Kjaergaard J, Clemmensen IH, Thomsen BL, Storm HH.
Validity of diagnoses of and operations for nonmalignant gynecological conditions in the Danish National Hospital Registry. Journal of clinical epidemiology. 2002;55(2):137-42.
71. Database DU. Danish Urogynaecological Database , annual report 2014 [12.08.2016]. 72. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. Scandinavian journal of public health. 2011;39(7 Suppl):38-41.

73. Løkkegaard EL, Johnsen SP, Heitmann BL, Stahlberg C, Pedersen AT, Obel EB, et al. The validity of self-reported use of hormone replacement therapy among Danish nurses. Acta obstetricia et gynecologica Scandinavica. 2004;83(5):476-81.

74. Wogelius P, Poulsen S, Sorensen HT. Validity of parentalreported questionnaire data on Danish children's use of asthma-drugs: a comparison with a population-based prescription database. European journal of epidemiology. 2005;20(1):17-22.

75. Schiøler G, Larsen OB. Klassifikation af operationer. 2 ed. Kbh.: Munksgaard Danmark; 2005. 388 sider p.
76. STROBE. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) 2016 [21.06.2016]. Available from: <u>http://www.strobe-</u>

statement.org/index.php?id=available-checklists. 77. International Classification of Diseases (ICD10),2004

### [31.08.2016]. Available from: http://www.who.int/classifications/icd/ICD-

### 10\_2nd\_ed\_volume2.pdf.

78. Birkmeyer JD, Sharp SM, Finlayson SR, Fisher ES, Wennberg JE. Variation profiles of common surgical procedures. Surgery. 1998;124(5):917-23.

79. Birkmeyer JD, Reames BN, McCulloch P, Carr AJ, Campbell WB, Wennberg JE. Understanding of regional variation in the use of surgery. Lancet. 2013;382(9898):1121-9.

80. Keyhani S, Falk R, Bishop T, Howell E, Korenstein D. The relationship between geographic variations and overuse of healthcare services: a systematic review. Med Care. 2012;50(3):257-61.

 Suskind AM, Kaufman SR, Dunn RL, Stoffel JT, Clemens JQ, Hollenbeck BK. Population based trends in procedures following sling surgery for urinary incontinence. International urogynecology journal. 2013;24(5):775-80.
 Wu MP, Long CY, Liang CC, Weng SF, Tong YC. Trends in reoperation for female stress urinary incontinence: A nationwide study. Neurourology and urodynamics. 2015;34(7):693-8.

83. Denman MA, Gregory WT, Boyles SH, Smith V, Edwards SR, Clark AL. Reoperation 10 years after surgically managed pelvic organ prolapse and urinary incontinence. American journal of obstetrics and gynecology. 2008;198(5):555 e1-5. 84. Clark AL, Gregory T, Smith VJ, Edwards R. Epidemiologic evaluation of reoperation for surgically treated pelvic organ prolapse and urinary incontinence. American journal of obstetrics and gynecology. 2003;189(5):1261-7.

85. Birkmeyer JD, Hamby LS, Birkmeyer CM, Decker MV, Karon NM, Dow RW. Is unplanned return to the operating room a useful quality indicator in general surgery? Arch Surg. 2001;136(4):405-11.

86. Halfon P, Eggli Y, Matter M, Kallay C, van Melle G, Burnand B. Risk-adjusted rates for potentially avoidable reoperations were computed from routine hospital data. Journal of clinical epidemiology. 2007;60(1):56-67.
87. Hansen MF, Lose G, Kesmodel US, Gradel KO. Reoperation for urinary incontinence: A nationwide cohort

study, 1998-2007. American journal of obstetrics and gynecology. 2015.

88. Spiegelhalter DJ. Handling over-dispersion of performance indicators. Qual Saf Health Care. 2005;14(5):347-51.

89. Andonian S, St-Denis B, Lemieux MC, Corcos J. Prospective clinical trial comparing Obtape and DUPS to TVT: one-year safety and efficacy results. European urology. 2007;52(1):245-51.

90. Araco F, Gravante G, Sorge R, Overton J, De Vita D, Sesti F, et al. TVT-O vs TVT: a randomized trial in patients with different degrees of urinary stress incontinence. International urogynecology journal and pelvic floor dysfunction. 2008;19(7):917-26.

91. Darai E, Frobert JL, Grisard-Anaf M, Lienhart J, Fernandez H, Dubernard G, et al. Functional results after the suburethral sling procedure for urinary stress incontinence: a prospective randomized multicentre study comparing the retropubic and transobturator routes. European urology. 2007;51(3):795-801; discussion -2.

92. Riva D SV, Tonta A et al. TVT versus TOT: a randomized study at 1 year follow up (abstract) Int Urogynecol J Pelvic Floor Dysfunct 2006.17((Suppl 2)):S93.

93. Betschart C, Scheiner D, Hess E, Seifert B, Fink D, Perucchini D. Patient satisfaction after retropubic and transobturator slings: first assessment using the Incontinence Outcome Questionnaire (IOQ). International urogynecology journal. 2011;22(7):805-12.

94. Heinonen P, Ala-Nissila S, Raty R, Laurikainen E, Kiilholma P. Objective cure rates and patient satisfaction after the transobturator tape procedure during 6.5-year follow-up. Journal of minimally invasive gynecology. 2013;20(1):73-8.
95. Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane database of systematic reviews (Online). 2015;7:CD006375.

96. Kenton K, Stoddard AM, Zyczynski H, Albo M, Rickey L, Norton P, et al. 5-year longitudinal followup after retropubic and transobturator mid urethral slings. The Journal of urology. 2015;193(1):203-10.

97. Stav K, Dwyer PL, Rosamilia A, Schierlitz L, Lim YN, Lee J. Risk factors of treatment failure of midurethral sling procedures for women with urinary stress incontinence. International urogynecology journal. 2010;21(2):149-55.
98. Miller JJ, Botros SM, Akl MN, Aschkenazi SO, Beaumont JL, Goldberg RP, et al. Is transobturator tape as effective as tension-free vaginal tape in patients with borderline maximum urethral closure pressure? American journal of obstetrics and gynecology. 2006;195(6):1799-804.
99. Houwert RM, Venema PL, Aquarius AE, Bruinse HW, Roovers JP, Vervest HA. Risk factors for failure of retropubic and transobturator midurethral slings. American journal of obstetrics and gynecology. 2009;201(2):202 e1-8.
100. Rud T. Urethral pressure profile in continent women from childhood to old age. Acta obstetricia et gynecologica

Scandinavica. 1980;59(4):331-5. 101. DeLancey JO. Structural support of the urethra as it relates to stress urinary incontinence: the hammock hypothesis. American journal of obstetrics and gynecology. 1994;170(6):1713-20; discussion 20-3.

102. Petros PE, Ulmsten UI. An integral theory of female urinary incontinence. Experimental and clinical considerations. Acta obstetricia et gynecologica Scandinavica Supplement. 1990;153:7-31.

103. Petros PE, Ulmsten UI. An integral theory and its method for the diagnosis and management of female urinary incontinence. Scand J Urol Nephrol Suppl. 1993;153:1-93.

104. Lose G, Brostrøm S. Urogynækologi. In: Ottesen B, Mogensen O, Forman A, editors. Gynækologi. 4. 1 ed.
Danmark: Munksgaard Forlag; 2011. p. 383-413.
105. Anger JT, Rodriguez LV, Wang Q, Pashos CL, Litwin MS. The role of provider volume on outcomes after sling surgery for stress urinary incontinence. The Journal of urology.
2007;177(4):1457-62; discussion 62.

106. Danish Health and Medicines Authorities. Revideret specialevejledning for gynækologi og obstetrik (version til ansøgning) [31.08.2016]. Available from:

http://sundhedsstyrelsen.dk/da/Feeds/~/~/media/E5EF5EF7 F66B484CBC2B5AC4F6401F81.ashx.

107. Van Baelen AA, Delaere KP. Repeat transobturator tape after failed mid-urethral sling procedure: follow-up with questionnaire-based assessment. Urol Int. 2009;83(4):399-403.

108. Tsivian A, Neuman M, Yulish E, Shtricker A, Levin S, Cytron S, et al. Redo midurethral synthetic sling for female stress urinary incontinence. International urogynecology journal and pelvic floor dysfunction. 2007;18(1):23-6. 109. Lee KS, Doo CK, Han DH, Jung BJ, Han JY, Choo MS. Outcomes following repeat mid urethral synthetic sling after failure of the initial sling procedure: rediscovery of the tension-free vaginal tape procedure. The Journal of urology. 2007;178(4 Pt 1):1370-4; discussion 4.

110. Monga AK, Robinson D, Stanton SL. Periurethral collagen injections for genuine stress incontinence: a 2-year follow-up. British journal of urology. 1995;76(2):156-60. 111. Frederiksen BL, Osler M, Harling H, Ladelund S, Jorgensen T. Do patient characteristics, disease, or treatment explain social inequality in survival from colorectal cancer? Social science & medicine (1982). 2009;69(7):1107-15.

Chapple CR, Haab F, Cervigni M, Dannecker C, Fianu-Jonasson A, Sultan AH. An open, multicentre study of NASHA/Dx Gel (Zuidex) for the treatment of stress urinary incontinence. European urology. 2005;48(3):488-94.
 Rothman KJ. Dealing with biases. Epidemiology : an introduction. 2 ed. Oxford New York: Oxford University Press; 2012. p. 124-47.

114. Porena M, Costantini E, Frea B, Giannantoni A, Ranzoni S, Mearini L, et al. Tension-free vaginal tape versus transobturator tape as surgery for stress urinary incontinence: results of a multicentre randomised trial. European urology. 2007;52(5):1481-90.

115. Drejer L, Hansen UD, Guldberg R. Procedure-og materialevalg ved urininkontinensoperationer i Danmark 2010-11.: DUGSNyt2; 2013.

116. Danish Health and Medicines Authorities. Notat om reoperationsrater. Contract No.: 2.7.2016.

117. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3 ed. Philadelphia: Wolters KluwerLippincott Williams & Wilkins.; 2008. x, 758 sider, illustreret p.