The Impact of Childbirth before and after Mid-Urethral Sling Surgery

New Knowledge derived from Norwegian Health Registries

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*Series of dissertations submitted to the
Faculty of Medicine, University of Oslo*

ISBN 978-82-8377-963-9

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Cover: Hanne Baadsgaard Utigard.
Print production: Reprosentralen, University of Oslo.

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ACKNOWLEDGMENTS

The present work was carried out at the Department of Gynaecology, Oslo University Hospital, from 2014 to 2021, with financial support from the Department of Gynaecology at Oslo University Hospital, Department of Obstetrics and Gynaecology at Bærum Hospital, and the Norwegian Medical Association.

This thesis represents a significant step forward in my academic career. Several key people have made this possible for me. First and foremost, I would like to express my heartfelt appreciation to my primary supervisor, Rune Svenningsen. I greatly appreciate your willingness to share your knowledge and expertise. Thank you for your enthusiasm and ongoing support throughout this project, and most importantly, thank you for keeping your door open at all times.

I would also like to thank Annetine Staff and Sigurd-Kulseng-Hanssen, my co-supervisors. Annetine, you are an inspiration to me, and your knowledge, drive, and capacity are impressive. Sigurd, I appreciate you introducing me to urogynaecology and clinical research.

My thanks go to Tomislav Dimovski, the system developer at the Norwegian National Female Incontinence Registry, for valuable help in extracting data from the Norwegian Female Incontinence Registry. I am also grateful for the support in the statistical analysis given by statistician Jon Michael Gran. Also, thanks to the contributory members of the Norwegian National Incontinence Registry at each reporting hospital department for help in recruiting women to my first study.

My gratitude also goes to Guri Majak for respecting the importance of research and preventing clinical tasks from interfering with my research time.

I would also like to express my gratitude to my amazing colleagues at the Department of Obstetrics and Gynecology at Ullevål hospital. You are my second family, and the collegiality at our department is unique. Thank you for all your cheering, encouragement, and discussions over the years.

Anne Birthe Lømo, thank you for allowing me to come to Elverum and work as a consultant with time designated for research when I needed a break from the work-life in Oslo.

My parents, Tone and Kåre. Thank you for your constant support and faith in me since my childhood. Thank you for always keeping me on a long leash and catching me when I fall.

Magnus, my husband. Every day, you make me a better person. Thank you for being the best father to our two children, Vera and Sigurd, my greatest gift in life. I thank them for simply being themselves and bringing joy and wonder into my life.

I'd like to express my gratitude to my mother- and father-in-law, Ragne and Hans Magnus. For all of their practical assistance in daily life, as well as all of the good care and love they bring into our home, making the realization of this thesis possible.

Last but not least. Thanks to all of the women who took part in the studies included in this thesis, as well as all of the patients I met during my clinical years. You are the ones who have taught me the most.

PUBLICATIONS INCLUDED IN THE THESIS

This thesis consists of three original papers, which are listed below. They will be identified by their Roman number.

I: Dyrkorn OA, Staff AC, Kulseng-Hanssen S, Schiøtz HA, Svenningsen R.

Childbirth after mid-urethral sling surgery: effects on long-term success and complications

Int Urogynecol J. 2020; 31: 485–492.

<https://doi.org/10.1007/s00192-019-04067-9>

II: Dyrkorn OA, Staff AC, Kulseng-Hanssen S, Dimoski T, Svenningsen R.

The completeness and accuracy of the Norwegian Female Incontinence Registry

Acta Obstet Gynecol Scand. 2020; 99: 1618–1625.

<https://doi.org/10.1111/aogs.13951>

III: Dyrkorn OA, Staff AC, Kulseng-Hanssen S, Svenningsen R.

Previous obstetrical history does not impact short-term mid-urethral sling outcomes

Int Urogynecol J. 2021; Online ahead of print.

<https://doi.org/10.1007/s00192-021-04836-5>

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ABBREVIATIONS

aOR	Adjusted odds ratio
BMI	Body mass index
CI	Confidence interval
EPINCONT	EPidemiology of INCONTinence in the county of Nord-Trøndelag
ICC	Intraclass correlation coefficient
ISD	Intrinsic sphincter deficiency
LAM	Levator ani muscle
MAR	Missing at random
MCAR	Missing completely at random
MNAR	Missing not at random
MoBa	Norwegian Mother-Child cohort study
MBRN	The Medical Birth Registry of Norway
MUCP	Maximum urethra closure pressure
MUI	Mixed urinary incontinence
MUS	Mid-urethral sling
N-Id	National identification number
NFIR	The Norwegian Female Incontinence Registry
NPR	The Norwegian Patient Registry
OAB	Overactive bladder
OR	Odds ratio
POP	Pelvic organ prolapse
PVR	Post void residual urine
PVS	Pubovaginal sling
Q _{max}	Maximum urinary flow rate
REC	The regional committee for medical and health research ethics
S-Id	Study identification number
SUI	Stress urinary incontinence
TOT	Trans-obturator tape (outside-in approach)

TVT	Tension-free vaginal tape
TVT-O	Tension-free vaginal tape-obturator (inside-out approach)
UBA	Urethral bulking agents
UI	Urinary incontinence
UTI	Urinary tract infection
UUI	Urgency urinary incontinence
VLPP	Valsalva leak point pressure
WHO	World Health Organization

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SUMMARY OF THE THESIS

Urinary incontinence (UI) is a common pelvic floor disorder, substantially impacting women's quality of life, productivity, socializing, and sexuality. Stress urinary incontinence (SUI), defined as “involuntary loss of urine on physical exertion, sneezing, or coughing”, is a subtype of urinary incontinence, affecting 10 – 39 % of the adult female population. SUI is most commonly found in women between 25 and 49 years of age. Insufficient support of the urethra is considered the primary underlying mechanism for SUI. These changes are believed to be induced by loss of or trauma to the connective tissue or muscular structures in the female pelvic floor. Childbirth, especially operative vaginal birth, is considered a significant risk factor.

In 1996, the mid-urethral slings (MUS) were introduced as a new surgical procedure to correct SUI, in which a synthetic mesh tape is implanted to support the mid-urethra. Today, MUS is considered the standard surgical treatment for SUI due to its high effectiveness, long-term durability, and lower repeat surgery rates than other surgical incontinence procedures. Conservative therapy is the preferred first-line treatment option, but surgical treatment is usually recommended if the woman has not achieved sufficient improvement.

Women, who have not completed childbearing, are usually advised to postpone surgical treatment, as a subsequent pregnancy is believed to impose a high risk of SUI recurrence. Secondly, there is no consensus regarding the preferred mode of delivery in a subsequent pregnancy. After a successful MUS operation, several surgeons will often recommend a cesarean delivery even though the scientific evidence is limited. Furthermore, we currently have little knowledge of whether a woman's history of childbearing and deliveries before an incontinence surgery with MUS could potentially impact the surgical result. Might it be possible that the same obstetrical risk factors leading to SUI also significantly impact the outcomes of a MUS operation after the completion of childbearing?

Norway and the Nordic countries have long traditions with mandatory notification to population-based central health registries. Over the last decades, medical quality registers have gained increased popularity in monitoring and improving the quality of health services. Several registries also include unique personal identifiers, enabling linkage between registries. Health registries have proved to be an essential source for research, but the value of a health registry extensively depends on the quality of the contained data. The Norwegian Female Incontinence Registry was established in 1998. The Registry has served as a source for several research projects. However, no studies had been conducted before this thesis to examine the registry's accuracy and completeness.

This thesis's main aim was to increase the knowledge of the potential clinical impact of pregnancies before and after mid-urethral sling operations. Norway has a birth registry covering all deliveries by mandatory notification (MBRN; Medical Birth Registry of Norway) and an extensive female incontinence quality registry (NFIR; Norwegian Female Incontinence Registry). Connecting these registries offers an opportunity to investigate associations that otherwise cannot be studied in randomized controlled trials for ethical and practical reasons. By combining data from these registries (from 1998 to 2016), we assessed the long-term subjective and objective clinical outcomes, including complications, in women with one or more completed pregnancies after MUS surgery. We could also examine if there were any differences in SUI recurrence risk based on the mode of delivery. Furthermore, we wanted to explore the potential impact of various obstetrical factors associated with SUI development on MUS surgeries' short-term subjective and objective failure rates. However, there was also a need to assess the data quality of the NFIR and ensure that the Registry was an acceptable research tool before we could rely on the results generated by such registry data. Consequently, the validation process of NFIR became the logical and necessary secondary aim of this thesis.

The long-term subjective outcomes and clinical complications in women with one or more childbirths after MUS were published in Paper I. In this

observational registry-based cohort study, women registered with childbirths after MUS during the years 1998 - 2016 were identified and invited to a follow-up study. The study included a case group of 72 women that had given birth after MUS. They were compared to a matched control group of women at a 1:3 ratio that underwent a MUS operation without subsequent childbirths. The women completed a structured telephone interview using a validated short-form urinary incontinence disease-specific questionnaire. The outcomes were subjective cure rate, symptom load if not cured (both stress and urgency incontinence symptoms), and any MUS-related complications during the pregnancy. The study revealed reassuring long-term subjective cure rates for women giving birth after MUS and comparable with the control group, regardless of delivery mode. In addition, we did not identify any long-term adverse effects of the MUS related to pregnancy and vaginal delivery. However, giving birth to more than one child after MUS was associated with a significant decline in SUI cure rates.

The data quality of NFIR was assessed by selecting a random sample of 300 women operated for urinary incontinence and reported to the Registry between 1998 and 2016 (with follow-up through 2017). We then compared data previously recorded in the national NFIR for ten selected key variables to the source data, which were the patient's medical record at the reporting hospital. The Registry's completeness was estimated by comparing surgical procedures registered in NFIR and the Norwegian National Patient Registry (NPR). The NPR is an administrative registry with a compulsory notification containing health-related data such as diagnoses and codes for surgical procedures. We found excellent accuracy for both continuous variables and categorical variables. The Registry's completeness has improved over time, and it now includes information on nearly all women in Norway who have received urinary incontinence surgery. The results from the evaluation of data accuracy and coverage were published in Paper II. We concluded that the registry data in NFIR were well suited for research and qualified for merging with data from the MBRN to answer our main aim for the thesis.

The impact of previous obstetrical history on the short-term subjective and objective failure rates after MUS surgery was examined in the third paper. Using merged data from NFIR and MBRN, a cohort of 14,787 women were included. We found that several obstetrical factors impacted both subjective and objective outcomes in the univariate logistic regression analyses. However, in the multivariate model, being nulliparous before MUS surgery remained the only significant risk factor and only for objective failure. In addition, constitutional factors, previously well documented in the literature, such as high body mass index (BMI) at time of surgery, non-retropubic slings, high preoperative urgency symptom load, and surgical complications, were all significant risk factors for both subjective and objective failure.

In conclusion, this thesis demonstrates that the Norwegian Female Incontinence Registry has a high degree of accuracy and is valid as a research tool. Furthermore, by using data from the Registry, we have shown that the long-term outcomes for women giving birth after MUS are reassuring, independent of delivery mode. Therefore, MUS seems to be a feasible option for women who have not completed childbearing. This conclusion, however, is likely most relevant in settings where the indication for surgery is strong and where conservative options have failed.

Also, we found that obstetrical factors associated with SUI development do not seem to impact the short-term outcomes of primary MUS operations. However, being nulliparous was an exception to this conclusion, indicating a different underlying SUI pathogenesis in these women.

We believe this thesis provides more accurate information on expected MUS outcomes in women with stress urinary incontinence, hopefully empowering both surgeons and women in the decision process when considering surgical treatment for SUI.

1 INTRODUCTION

Urinary incontinence is a common pelvic floor disorder, substantially impacting women's quality of life, productivity, socializing, and sexuality [1, 2]. This introductory chapter will present the current definition of urinary incontinence, followed by normal continence mechanisms, current knowledge regarding the pathophysiology of SUI, as well as an overview of different treatment options. Finally, the current knowledge on the effects of pregnancy and delivery on the urinary continence mechanism will be discussed.

In previous studies, pregnancy and delivery have primarily been associated with an increased risk of stress urinary incontinence [1, 3–8]. However, the correlation to other forms of incontinence has been less evident. For this reason, the emphasis of this section will be on SUI. A complete description of the impact of pregnancy and delivery on the risk of pelvic floor disorders is beyond the scope of this thesis.

1.1 Definitions of urinary incontinence

Urinary incontinence (UI) encompasses a range of different symptoms which may differ in frequency and severity. A widely used definition, as stated in the joint terminology report from the International Urogynecological Association (IUGA) and the International Continence Society (ICS) in 2010, is “the complaint of any involuntary leakage of urine” [9]. The type of incontinence can be classified subjectively by patient-reported symptoms or objectively by clinical signs and urodynamic investigations. The symptom-based terminology of UI and UI forms as described in this report is shown in

Table 1.

Stress urinary incontinence is defined as the involuntary loss of urine that occurs synchronously with an increase in intraabdominal pressure (e.g., with exertion, sneezing, coughing, and laughing) [9]. Urodynamic stress urinary incontinence may be observed during a urodynamic investigation and is defined as involuntary loss of urine from an increase in intra-abdominal pressure, which overcomes the resistance of the bladder outlet in the absence of a detrusor contraction [9].

Urgency urinary incontinence (UUI) is defined as involuntary urinary leakage accompanied by or immediately preceded by urgency (complaint of a sudden, compelling desire to pass urine which is difficult to defer) [9]. UUI is usually diagnosed based on the patient-reported symptoms but can also be objectively diagnosed by observations of uninhibited detrusor contractions during bladder filling when performing a urodynamic examination [9]. UUI is part of a symptom complex known as overactive bladder syndrome, characterized by urinary urgency with or without incontinence in the absence of urinary tract infection or other apparent diseases. It is frequently accompanied by urinary frequency and nocturia [9]. Mixed urinary incontinence (MUI) is a combination of UUI and SUI [9].

Table 1: Definition of UI symptoms according to ICS/IUGA 2010 [9]

Type of UI symptoms	Type of UI symptoms
Urinary incontinence	Complaint of any involuntary loss of urine
Stress urinary incontinence	Complaint of involuntary loss of urine on effort or physical exertion (e.g., sporting activities) or on sneezing or coughing
Urgency urinary incontinence	Complaint of involuntary loss of urine associated with urgency
Mixed urinary incontinence	Complaint of involuntary loss of urine associated with urgency, and also with effort or physical exertion or on sneezing or coughing
Postural urinary incontinence	Complaint of involuntary loss of urine associated with change of body position, for example, rising from a seated or lying position
Nocturnal enuresis	Complaint of involuntary loss of urine which occurs during sleep
Continuous urinary incontinence	Complaint of constant leakage of urine
Insensible urinary incontinence	Complaint of urinary incontinence where the woman has been unaware of how it occurred
Coital urinary incontinence	Complaint of involuntary loss of urine with coitus

1.2 Epidemiology

Accurate prevalence or incidence rates for incontinence are difficult to ascertain due to heterogeneous data sampling methods and definitions of urinary incontinence. For example, some studies combine nulliparous and parous women, whereas others treat these groups separately. Furthermore, incontinence is a stigmatizing condition in many populations, and some women might be reluctant to disclose their symptoms [10].

In extensive population-based studies, it has been demonstrated that female incontinence is highly prevalent, with any UI ranging between 25 % and 45 % and daily UI between 5 % and 15 % [11–13]. The prevalence of SUI has shown a peak at menopause, with a prevalence of 30 % among women aged 50 to 54 years, while MUI and UUI continue to increase with advancing age [12]. SUI is the most commonly reported subtype of incontinence representing approximately half of the women with incontinence, followed by MUI and then UUI [11–13]. As reviewed by the 6th International Consultation on Incontinence, the prevalence of SUI ranges from 10 % to 39 % of the adult female population and is most commonly found in women between 25 and 49 years of age [1]. MUI and UUI are more common in older women, with a reported prevalence of 7.5 % to 25 % and 1 % to 7 %, respectively [1].

1.3 Female urinary continence mechanism

Female urinary continence is maintained by a normal storage function of the urinary bladder, urethral closure function, and anatomical support from the pelvic floor. Damage or changes in any of these functions may result in different symptoms, depending on the origin. In this thesis, only factors related to stress urinary incontinence (SUI) development will be reviewed.

The female urethra and surrounding structures have an essential role in the urinary continence mechanism. A comprehensive description of the urethral anatomy and continence mechanisms is supplied in a recent review by Mistry et al. from 2020 [14]. The urethra is a tubular structure composed of two layers of smooth muscles (an inner longitudinal layer and an outer circular layer) [15]. The smooth muscles are found in the proximal part of the urethra and are innervated by the autonomous nervous system [16]. The external urethral sphincter, composed of circular striated muscles, surrounds the urethra and extends from the bladder neck to the perineal membrane [17]. It

consists of three different muscles: m. sphincter urethrae which surround the proximal two-thirds of the urethra, m. compressor urethrae and the m. urethrovaginal sphincter connects to the vaginal wall and the ischiopubic ramus and surrounds the distal third of the urethra [18]. These three muscles form a sleeve around the urethra, with the most condensed portion in the mid-urethra, also known as the high-pressure zone [19]. The external urethral sphincter is innervated by both the autonomous and somatic nervous systems, suggesting a joint function with the bladder, bladder neck, and urethral smooth muscles [16].

Continence is dependent on the urethra's ability to maintain a sufficient urethral closure pressure during rest and intra-abdominal pressure fluctuations [19, 20]. This pressure is maintained by active and passive closure mechanisms in the urethra and supportive structures adjacent to the urethra. Connective tissues, mucosal vessels, tonic contraction of the m. levator ani and neuronal stimuli of smooth muscles are mechanisms that provide permanent closure during rest [15]. In situations where the intra-abdominal pressure increases, additional support is provided by activating the external urethral sphincter and muscles in the pelvic floor [21].

1.4 Stress urinary incontinence pathophysiology

Different theories on the pathophysiological mechanisms of SUI have been proposed and have been developed together with various surgical techniques trying to restore the normal anatomy of the urethra. Two different pathophysiological mechanisms are currently considered to be explanatory for the development of SUI. These mechanisms are not mutually exclusive and might coexist to a variable degree.

1.4.1 Hypermobility of the urethra

Hypermobility of the urethra is caused by insufficient support of the urethra from the vaginal wall, connective tissue, or pelvic floor muscles [22–24].

During physical exertion, sneezing, or coughing, the intra-abdominal pressure increases, and the urethra fails to remain closed, leading to leakage of urine. Insufficient support may be due to loss of connective tissue, decreased muscular strength, or trauma.

The integral theory, introduced in 1990 by Petros and Ulmsten, proposed that SUI and pelvic organ prolapse development is related to an increased tissue laxity of the vagina or its supporting structures [25]. The theory was based on an anatomical understanding that urethra closure occurs due to synergistic actions between pelvic muscles and supporting ligaments. Important factors for maintaining urinary incontinence are the pubourethral ligament, which attaches the urethra to the pubic bone, and the levator ani muscle and pubococcygeus muscles [25, 26]. During increased intra-abdominal pressure, the bladder outlet is closed by a contraction of the pubococcygeus muscles and the levator ani muscles, supported by the pubourethral ligaments. According to Petros and Ulmsten, damage or alterations of the suspending ligaments could cause dysfunction in the closure mechanism of the urethra, resulting in SUI [25, 26].

In 1994, DeLancey introduced the hammock theory [27]. Anatomical studies on cadavers demonstrated that mid-urethral support is provided by the anterior vaginal wall, suspended by fascial attachments to the levator ani muscle at the arcus tendineus fasciae pelvis. These musculofascial structures create hammock-like sub-urethral support that enables compression of the urethra when the intra-abdominal pressure increases, maintaining continence. Conversely, if the mid-urethral support is reduced or damaged, the urethra will move downwards without being compressed, and the

pressure in the bladder will overcome the pressure in the urethra, resulting in leakage [28, 29].

1.4.2 Intrinsic sphincter deficiency

The second mechanism for SUI is a loss of proximal urethra closure function, which could be due to reduced urethral mucosa or muscular tone in the urethral sphincter [30, 31]. Patients with intrinsic sphincter deficiency (ISD) often experience leakage with minimal intra-abdominal pressure or continuous leakage. Pelvic surgery, hypoestrogenism, aging, and neurological disease are conditions associated with the condition [32, 33]. ISD was initially proposed to explain failure after surgical treatment and the presence of SUI in the absence of urethral hypermobility. However, there has been a shift away from this definition, and ISD is now diagnosed using urodynamic examinations. Currently, there are no standardized criteria for the diagnosis of ISD, but finding a maximal urethral closure pressure (MUCP) < 20 cm H₂O or a Valsalva leak-point pressure (VLPP) of < 60 cm H₂O are proposed as criteria for ISD [34].

1.5 Risk factors for stress urinary incontinence

1.5.1 Obstetrical factors

Pregnancy, increasing parity, and vaginal delivery have all been identified as risk factors for stress urinary incontinence (SUI). Cohort studies have found that SUI is more prevalent in women who have had at least one child, supporting a causal role of pregnancy and delivery [1, 3–8]. It has been estimated that 50 % of SUI risk can be attributed to pregnancy and vaginal delivery [35].

In the EPINCONT-study (EPidemiology of INCOntinence in the county of Nord-Trøndelag), a large cross-sectional study including 27,900 women, parity was

highly associated with urinary incontinence, with the first delivery being the most significant [3]. Furthermore, in the age group 20 to 34, the relative risk of having SUI was significantly increased for parous women compared with nulliparous women (RRs 2.2 for primiparous and 3.3 for grand multiparous women). However, the impact of parity seemed to diminish over time, with no effect on the age group over 65 years.

Several studies have found a higher prevalence of SUI after vaginal delivery than after cesarean delivery [5, 6, 8, 36–40]. For example, a systematic review of 15 studies reported an almost two-fold increase in the risk of developing SUI following a vaginal delivery than cesarean delivery [41]. However, there is controversy regarding the protective effect of cesarean deliveries on SUI, as studies have demonstrated that the effect on SUI development later in life diminishes over time and disappears after multiple deliveries [8, 37, 40].

The evidence of the impact of operative vaginal deliveries on the risk of developing SUI is conflicting [8, 41–44]. A systematic review from 2016 (with five relevant studies) found no difference in SUI prevalence between operative and spontaneous vaginal delivery [41]. Currently, only one study has compared forceps and vacuum delivery separately for the risk of SUI. In a large population-based study (The Nord-Trøndelag Health Study - HUNT), forceps delivery was associated with a nearly twofold increase in long-term risk of SUI among women younger than 50 years compared to women with spontaneous vaginal delivery [42]. However, no measurable impact of forceps was found among women aged 50 and up, indicating that other factors will have a more significant impact as age increases. In the same study, vacuum delivery was not associated with an increased risk of SUI compared to spontaneous vaginal delivery [42].

There is conflicting evidence for the relationship between fetal proportions and SUI [5, 45–48]. Wesnes et al. examined the impact of fetal size (head circumference and weight) using data from the Norwegian Mother-Child cohort study (MoBa) combined with data from the Medical Birth Registry. A cohort of 7,561 primiparous women who were continent before and during pregnancy were assessed for UI of any type. Birthweight 3,500 – 4,200 g was significantly associated with a higher risk of SUI 6 months postpartum, while head circumference > 36 cm was associated with a higher risk of UUI [47]. Similar associations were also found in a study using data from the EPINCONT study [48].

Several studies have demonstrated an association between increasing maternal age and SUI risk [6, 8, 45, 49]. For example, a large Swedish register-based study, including 90,000 women aged 30 years and above at their first delivery, was associated with an increased risk of SUI surgery later in life, regardless of delivery mode (4.9 vs. 3.2 pr. 10,000 person-years) [49].

1.5.2 Obesity

A strong association between obesity and SUI and UUI has been found in numerous studies. Obese women have approximately two times the risk of SUI compared to non-obese women [7, 50, 51]. Increased intra-abdominal pressure due to obesity, adversely stressing the pelvic floor, has been demonstrated to be an underlying pathophysiological mechanism for SUI development [50, 51]. Obesity is a modifiable risk factor. Observational studies for surgical and non-surgical weight loss have shown a reduction in SUI of 50 % or more, depending on the degree of weight loss [52–54].

1.5.3 Age

In a large cross-sectional study in Norway, including 11,397 women, the prevalence of incontinence of any type increased with increasing age [12].

However, for SUI, a distinct peak was observed around menopause. Similar observations have been seen in other population-based studies [11, 13]. Furthermore, studies have shown that the patient-reported prevalence of genuine SUI decreases after menopause [12, 55]. One possible explanation for this observation may be that bother from SUI is masked due to the increasing incidence of UUI.

1.5.4 Connective tissue

Studies have demonstrated the role of connective tissue quality and pelvic floor dysfunction. Abnormalities in the quantity, quality, and type of collagen have been observed in women with SUI. Mutations in the gene for collagen type I have been found to be associated with SUI [56]. Kean et al. demonstrated that nulliparous women with SUI had less collagen in sub-urethral biopsies than a continent control group [57].

1.5.5 Pelvic surgery

Hysterectomy is an independent risk factor for SUI [58, 59]. The pathophysiological mechanism is poorly understood, but damage to the pelvic nerves or support structures during the surgery has been proposed as an underlying mechanism [58]. SUI is frequently associated with pelvic organ prolapse (POP), but it may not appear until after the prolapse has been treated surgically [60]. This phenomenon is known as occult incontinence or SUI on prolapse reduction [9]. Advanced POP is believed to induce urethral kinking with increased bladder outlet obstruction and potentially masking SUI [61].

1.6 Surgical treatment of stress urinary incontinence

Surgical treatment for female SUI is usually recommended when conservative treatment has failed. Numerous surgical procedures have therefore been

developed with different approaches to restoring continence. Some surgical methods have aimed at creating urethral compression (e.g., Kelly), some the restoration of the retropubic position of the urethra (e.g., Burch colposuspension). Some aim to increase the intrinsic urethral coaptation (e.g., bulking agents), and lastly, some aim to create a hammock-like structure, in which the urethra can be compressed during increased intra-abdominal pressure (mid-urethral slings - MUS).

1.6.1 Historical background

In 1914, Kelly et al. published an article describing an operative procedure for SUI treatment involving plication of the bladder neck with interrupted mattress sutures [62]. Combined with an anterior colporrhaphy, this procedure became the standard SUI procedure for 60 years, with long-term success rates up to 65 %.

A new technique was described in 1949 by Marshall, Marchetti, and Krantz, which involved stabilizing and restoring the proximal urethra in a retropubic position by lifting the tissue near the bladder neck and proximal urethra [63]. In 1961, Jon Burch published an article describing a similar abdominal approach, where the paravaginal tissue is sutured to the Coopers ligament, creating a suspension for the vesicourethral segment [64]. The procedure has later been modified to be performed with laparoscopic or robot-assisted technique. Burch colposuspension has been shown to be an effective treatment for primary and recurrent SUI, with short-term cure rates between 67 % and 71 %. However, the surgical result often deteriorates over time, with long-term cure rates between 36 % and 52 % [65].

In 1942, Aldridge reported a procedure using the patient's fascia to support the urethra [66]. This procedure was the forerunner of the autologous fascial pubovaginal sling (PVS), using either fascia obtained from the abdominal

rectus fascia or tensor fascia lata. These slings are usually placed under the proximal urethra or bladder neck using an abdominovaginal approach. The implanted graft material will then provide a compressive force on the urethra or re-establish the suburethral hammock that the urethra is compressed against during increased intra-abdominal pressure. Other materials have also been used, such as xenografts and different synthetic materials (not polypropylene like used in MUS). However, these materials placed under the proximal part of the urethra have been associated with poorer outcomes than autologous tissue [65]. Nevertheless, the technique was popularized after McGuire and Lytton in 1978 reported an 80 % success rate in patients treated with PVS for intrinsic sphincter deficiency [67]. The use of PVS with autologous fascia has been evaluated in a systematic review including 1,280 women, with long-term cure rates that included both subjective and objective evaluations ranging from 73 % to 95 % [68].

1.6.2 Mid-urethral slings

Burch colposuspension and PVS were considered the gold standard operations for SUI treatment for many years. However, these techniques were invasive, time-consuming, and had high rates of postoperative complications. Therefore, several attempts were made to reduce the invasiveness of SUI procedures and to limit patient morbidity. Traditionally, incontinence procedures aimed to suspend or add support to the distal urethra or the bladder neck. During the 1990s, the importance of mid-urethral support became more evident with the proposal of the integral theory by Petros and Ulmsten [25] and the hammock theory introduced by DeLancey [27]. According to these theories, the support of the mid-urethra by the pubourethral ligaments creates a physiological backboard that enables compression of the urethra during increased intra-abdominal pressure. If the backboard is damaged or absent, this could promote the development of SUI.

Ulmsten and Petros described further a rationale for placing a sling of supporting material under the mid-urethra that could theoretically replicate the action of the backboard [69].

In 1996, the tension-free vaginal tape (TVT) was introduced as a new surgical technique for SUI, performed under local anesthesia, with short operative time and minimal surgical dissection [70]. A sling of polypropylene mesh (approximately 1 cm in width) is inserted through an anterior vaginal wall dissection at the level of mid-urethra and placed retropubically through the lower abdominal wall with specially designed trocars. Before closing the anterior wall, the sling is left tension-free under the urethra, avoiding compression of the urethra. The technique was later modified to include an alternative trans-obturator route (inside-out approach - Tension-free Vaginal Tape-Obturator [TVT-O] and an outside-in approach - Trans-Obturator Tape [TOT]) [71, 72].

The mechanism of action of mid-urethral slings has been demonstrated by using ultrasound and urodynamics. When the intra-abdominal pressure increases, the tape rotates towards the pubic bone, compressing the urethra and the surrounding tissue against it [73, 74]. Urodynamic evaluations have demonstrated that MUS increases the pressure transmission ratio along the urethra while the maximum urethra closure pressure at rest remains unchanged [75, 76]. Similar results were obtained using urethral pressure reflectometry, indicating that MUS improves urethral closure function by increasing adjunctive closing forces, providing increased resistance to urethral dilatation [77, 78].

Mid-urethral slings (MUS) have become popular due to their high efficacy, long-term durability, and low morbidity. They are currently considered the preferred procedure for surgical correction of SUI. The latest Cochrane

review on surgical treatment of SUI (2017) concluded that over 80 % of women with stress urinary incontinence were cured or had significant improvement in their symptoms at medium- to long-term follow-up after MUS [79]. Furthermore, the authors found similar subjective- and objective cure rates for retropubic and trans-obturator routes, but the obturator route seemed to have higher rates of reoperations due to SUI recurrence compared with the retropubic route (RR 8.8, 96 % CI 3.4 – 23.0).

In recent years, there have been public concerns about the use of mesh in gynecological procedures. In 2008, the Food and Drug Administration (FDA) in the US issued a public health notification cautioning against the use of synthetic mesh implants in the correction of pelvic organ prolapse (POP) and SUI [80]. The most frequent complications reported after mesh use were vaginal erosions, pain, infections, dyspareunia, and urinary-related symptoms, with reported adverse outcome rates as high as 30 % after POP repairs [81, 82]. In a 2011-update, FDA stated that most mesh-related complications were associated with transvaginal repairs of POP, and no evidence favored vaginal mesh repair over native tissue repair [80]. At that time, there was insufficient data to warn against using synthetic mesh implants in SUI-procedures. In contrast to POP repair with synthetic mesh, there seem to be lower complication rates after MUS. Studies of adverse effects of MUS have reported mesh-related complications in 2.1 % to 2.4 % [83]. Although rare, there has been a concern that complications after MUS are under-reported and might occur several years after the surgery [84]. Since 2018, the use of any vaginal mesh type, including synthetic implants for SUI, has been temporarily restricted in the United Kingdom until further long-term safety data are available [85]. In 2019, FDA ordered the withdrawal of all vaginal synthetic mesh implants used for POP repairs in the USA [80]. The

use of synthetic mesh implants for SUI surgery, however, remains controversial worldwide.

1.6.3 Urethral injection therapy

Urethral bulking agents (UBA) are injectable materials placed around the bladder neck to restore the mucosal coaptation of the urethra during increased intra-abdominal pressure. Several different injectable materials have been developed, with synthetic non-absorbable gels most widely used. The procedure is minimal-invasive, requiring only local anesthetics, and can be done in an outpatient setting. Two injections might be necessary to achieve a durable result. In a randomized study comparing UBA with MUS, objective cure rates were 66 % vs. 95 % at one-year follow-up [86]. Long-term subjective cure rates have been reported between 44 % and 67 % [87, 88]. Although less effective than surgery, the procedure may be a feasible option for women with multiple comorbidities who have already had a MUS or cannot undergo surgery for other reasons. With the current controversy related to non-absorbable mesh in sling surgery, UBA has gained a renewed interest as an alternative to MUS.

1.6.4 Childbirth and mid-urethral sling surgery

Childbearing has a strong causal relationship with the development of SUI. There is, however, limited evidence on how or if pregnancy and delivery potentially also impact the outcomes of incontinence surgery.

Although most women with bothersome SUI are postmenopausal, studies have reported that SUI occurs in 5 % to 14 % of women of fertile age [3, 11, 12]. Women in this age group with severe SUI symptoms may request surgical treatment for their incontinence bothers. Plans for future pregnancies have been considered a relative contraindication for surgical treatment of SUI [89]. Because pelvic support might be injured during pregnancy and vaginal

delivery, a successful MUS operation is thought to carry a high risk of SUI recurrence if followed by a pregnancy [90]. It has also been hypothesized that anatomical changes that occur during pregnancy and delivery could potentially alter the position of the incontinence tape, leading to recurrence of SUI or complications such as voiding dysfunction, recurrent urinary tract infections, erosions, or injuries to the urethra [91, 92]. Consequently, many surgeons would recommend cesarean delivery for women who have had prior incontinence surgery [93]. However, the scientific evidence has been based on small case series, without a control group (non-exposed women), and limited follow-up time [94–97]. Due to a lack of data, there is currently no established best practice on managing a pregnancy or the preferred mode of delivery when a woman presents with pregnancy after previous MUS surgery.

1.7 Non-surgical treatment options for SUI

Conservative treatment options are frequently used as the first-line treatment for mild to moderate degrees of SUI.

1.7.1 Pelvic floor muscle training

Pelvic floor muscles have a crucial role in maintaining the continence mechanism. Regular pelvic floor muscle training has a high level of evidence as a treatment option for mild to moderate SUI. According to a systematic review of randomized trials, women who received supervised pelvic floor muscle training were more likely to report improvement or cure for any type of incontinence when compared to those who did not (67 % vs. 29 % and RR 2.39, 95 % CI 1.64 – 3.47) [98].

1.7.2 Vaginal devices

Vaginal pessaries are firm yet flexible mechanical aids that improve urethral support. They can benefit patients who experience stress incontinence during specific activities or situations and might be an alternative for women who want to avoid or postpone surgery for medical or personal reasons. In a large randomized study, the overall patient satisfaction rate was approximately 50 % for women assigned to vaginal pessaries [99]. Other disposable and non-disposable vaginal devices have been developed and are inserted like a tampon before women engage in activities that typically otherwise result in urine leakage.

1.8 Childbearing and the pelvic floor

Pregnancy and delivery continue to be the most stressful and dangerous event the female pelvic floor is subjected to during a women's lifespan. Pelvic floor dysfunction, including stress urinary incontinence (SUI), pelvic organ prolapse (POP), and anal incontinence, are all associated with pregnancy and delivery. Several mechanisms related to how pregnancy and delivery impact the pelvic floor have been studied. However, the mechanisms have not been entirely determined, and there is still controversy about how pregnancy and delivery might cause pelvic floor dysfunction. In this section, the main focus will be on the pathophysiological mechanisms related to SUI.

1.8.1 Pregnancy and pelvic floor function

The pelvic floor is subjected to reversible and irreversible anatomical, morphological, functional, and hormonal changes during pregnancy. Unfortunately, many of these mechanisms remain unknown as research assessing the effect of pregnancy on the pelvic floor is scarce and mainly performed on animal models.

Hormonal changes examined during pregnancy include relaxin, estradiol, progesterone, and cortisol [100–102]. Heightened progesterone levels have been found to increase the relaxation of muscles and fibromuscular structures [100]. Low levels of relaxin are associated with an increased risk of UI during pregnancy [101]. Ashton-Miller et al. found alterations in the collagen structure during pregnancy, using a rat model, demonstrating an increase of the viscoelastic properties of the vaginal wall and pelvic floor muscles, presumable to allow genital stretching during vaginal delivery [103]. However, more comprehensive data on the effect of pregnancy on the qualitative properties of human pelvic floor tissue are lacking.

As the pregnancy develops, the increased weight on the pelvic support structures induces anatomical changes on the pelvic floor, urethra, and bladder neck. Dietz et al. have demonstrated significant changes in voiding function for a cohort of primigravida women examined during pregnancy by ultrasound and urodynamics [104]. During the second trimester, an increase in the angle between the bladder neck and the urethra compared to non-pregnant women was observed. As the pregnancy developed, an increased bladder neck mobility was also identified [104–106]. These findings were also confirmed by Stær-Jensen et al. in a prospective cohort study examining nulliparous women 21 weeks and 37 weeks of gestation [107].

Functions maintained by the pelvic floor might start to fail during pregnancy. As a result, women might experience their first symptoms of urinary incontinence (UI) during pregnancy, or preexisting incontinence might increase in severity. In the Norwegian Mother-Child cohort study (MoBa), including 43,279 women, the prevalence of any type of UI increased from 26 % before pregnancy to 58 % in the third trimester [108]. The most common UI type was stress urinary incontinence (SUI), reported by 31 % in the nulliparous group and 42 % in the parous group [108]. Urinary incontinence

might persist after giving birth. In a systematic review, including 33 studies, about one-third of the women experienced urinary incontinence (any type) during the first three months postpartum [36]. Parity, age, body mass index, and birth weight were significantly associated with persistent UI postpartum [36, 108–110]. Women who develop UI during pregnancy generally have a good prognosis as symptoms are likely to resolve after delivery for most women [36, 111]. For women with persistent UI after delivery, the degree of UI decreases during the first year postpartum, with a significant reduction of frequencies of incontinence episodes and severity of bother [112]. However, it appears that the temporary physiological changes occurring during pregnancy may perhaps reveal women prone to incontinence later in life [113, 114]. Long-term follow-up studies have demonstrated an increased risk of SUI later in life for women with incontinence during pregnancy, with minor modification by mode of delivery [113, 114].

1.8.2 The effect of vaginal delivery on pelvic floor function

The pelvic organs are supported by the endopelvic fascia and pelvic muscles, requiring an intact nerve supply. During vaginal delivery, the bony fetal head stretches the pelvic floor muscles, fascia, and nerves as it emerges through the birth canal. Reversible or permanent injuries to pelvic structures might occur by direct laceration or ischemia due to compression.

The main components of the pelvic diaphragm are the levator ani muscle (LAM) and the endopelvic fascia, which form a U-shaped complex around the pelvic outlet that keeps the urogenital hiatus closed and resist vaginal downward displacement during increased intraabdominal pressure. During vaginal delivery, the pelvic floor is stretched substantially to allow the passage of a baby. According to simulation models, pelvic muscles are stretched up to 3.3 times their length during the second stage of labor, which is more than double the length observed without injuries in non-gravida

passively stretched striated muscle [103]. Several ultrasound studies have examined the effect of pregnancy and delivery on the LAM [106, 107, 115–118]. Vaginal delivery is associated with a larger, more distensible levator hiatus [106, 119, 120]. Loss of levator function may be seen on ultrasound examinations as widening of the urogenital hiatus and may be observed after both cesarean and vaginal deliveries [116, 119]. During vaginal delivery, the LAM may be torn from its insertion at the pubic bone (avulsion). In primiparas, the prevalence of levator avulsion has been reported to range between 13 and 22 % [115, 117]. Risk factors for levator avulsions include fetal head circumference ≥ 35.5 cm, a prolonged second stage of labor, and operative vaginal deliveries [118, 121–123]. Several studies have demonstrated that LAM avulsions are strongly associated with reduced pelvic floor strength and pelvic organ prolapse, particularly in the anterior vaginal compartment [124–127]. However, there does not appear to be a strong association between LAM avulsions and SUI development [128–131].

Several studies have demonstrated persistent bladder neck and urethral mobility changes after delivery [119, 120, 131, 132]. These changes may persist or recover during the first year after delivery [119, 120]. Hypermobility of the bladder neck has been observed independently of delivery mode, and the findings on the effect of delivery mode have been contradictory [119, 120, 131]. A few studies have examined whether LAM avulsions affect bladder neck mobility [131, 133, 134]. Volløyhaug et al. prospectively followed a cohort of 180 women from pregnancy and up to four years postpartum [131]. The authors found an increased bladder neck and urethral mobility, independently of delivery mode. Still, women with LAM avulsions had a larger increase in bladder neck descent than women without LAM injuries [131]. However, the proportion of UI in women with LAM avulsions did not differ from the group without LAM avulsions, but these

findings might indicate a higher long-term risk of UI development after such avulsions.

During the second stage of delivery, the fetal head may also cause stretching and compression of nerves innervating the pelvic floor, leading to denervation and weakening of the pelvic floor [135]. Simulation models have demonstrated that the pudendal nerve is stretched well beyond the nerve injury threshold [136]. In addition, neurophysiological tests have shown denervation of the anal sphincter and levator muscle, supporting this mechanism of injury. Operative delivery, a prolonged second stage of labor, and high birth weight are all risk factors associated with pudendal nerve damage [137]. Fortunately, studies suggest that neuromuscular injuries resolve during the first years after delivery for the majority of women [138], which could explain the spontaneous resolution of SUI during the same period.

1.9 The Norwegian Female Incontinence Registry

The Norwegian Female Incontinence (NFIR) registry was established in 1998, shortly after the introduction of the tension-free vaginal tape (TVT) [139]. The procedure gained popularity and was soon performed at the majority of gynecological departments in Norway. However, in the beginning, there was a limited amount of data on outcomes and complications. Consequently, the Norwegian Urogynecology Group was founded to increase the scientific interest in urogynecology and create a tool for monitoring and evaluating SUI surgery outcomes. Twenty-three gynecological departments were associated with the Registry after its inception on September 1st, 1998.

Preoperative patient-reported data and objective clinical and urodynamic data and the type of incontinence procedure and complications are reported to the Registry. The patients are also evaluated 6 to 12 months and three

years after surgery either by a physical follow-up for both subjective and objective data or by telephone or postal form for subjective data. The patient-reported data and results from objective and urodynamic testing at the follow-ups are reported to the Registry. The same validated short-form urinary incontinence disease-specific questionnaire in Norwegian is used to retrieve subjective data before surgery and at all subsequent follow-ups [140]. For more detailed information on the validated questionnaire, please see Chapter 3.4. The data are entered into a local database at each reporting hospital unit. From there, data are exported in a de-identified form electronically to the NFIR two-three times yearly. Thus, the patients' identities are always kept secure at the reporting hospital. The patients sign a consent form for the transfer of data to the National Registry. Women cannot abstain from registration in the local database at the hospital unit performing the surgery but can opt-out from having their data exported in de-identified form to the national registry. If they do not consent, the data are exported anonymously for purely statistical purposes, but the data are not traceable. The registry creates and distributes annual reports to the reporting hospital units on patient outcomes and complication rates for both the reporting department as a whole and at the level of the individual surgeon. In these reports, the hospital units are compared to a national average on a variety of outcomes. Similar registries have later been established in other countries (Netherlands 2000, UK 2000, Denmark 2006, Sweden 2006).

Since 2016, all public hospitals in Norway that perform female incontinence surgeries have been instructed by their Regional Health Authority to report their data to the registry. As a result, from 2017, complete coverage of all 38 public hospitals performing this type of surgery has been achieved [141]. In addition, one private hospital (Betanien Hospital in the Bergen area) regularly reports their incontinence surgeries to the Registry.

2 AIMS OF THE THESIS

This thesis's main aim was to increase knowledge of whether undergoing pregnancies before or after mid-urethral sling operations for urinary stress incontinence have an impact on the clinical outcome. Furthermore, we wanted to assess the data quality of the national Norwegian Female Incontinence Registry to ensure that the Registry represents a reliable tool for quality control and scientific research.

The specific aims of each paper were to:

1. Evaluate the long-term subjective outcomes in women with one or more childbirths after mid-urethral sling (MUS) surgery, and evaluate any potential differences in clinical outcomes based on the mode of delivery in women with one or more childbirths after MUS surgery (Paper I).
2. Validate the accuracy of ten key variables in the Norwegian Female Incontinence Registry and examine whether there have been differences in data accuracy over time and based on the reporting hospitals' surgical volume. Furthermore, the study aimed to document the completeness and coverage of the Registry (Paper II).
3. Investigate the potential impact of various obstetrical factors associated with SUI development on the short-term subjective and objective failure rates for primary MUS surgery performed after the completion of childbirths (Paper III).

3 MATERIAL AND METHODS

3.1 Study design

Paper I

To examine the impact of pregnancy after mid-urethral sling (MUS) operations, a matched cohort study design was selected, where an exposed person is compared with one or more unexposed individuals. Longitudinal data (three data collecting points) prospectively collected by the Norwegian Female Incontinence Registry (NFIR) linked with data from the Medical Birth Registry of Norway (MBRN) were used. Participants included in the study underwent a structured telephone interview using a validated short-form urinary incontinence disease-specific questionnaire, and additional demographic and clinical information was collected. Women who had delivered one or more children after MUS surgery were compared with women without subsequent deliveries after MUS.

Paper II

This was a validation study of the NFIR. A random selection of women from NFIR was extracted to validate ten selected key variables' accuracy using the women's medical records at their local hospital department as a gold standard measure (source data). In addition, the Registry's completeness, defined as the proportion of women with a urinary incontinence operation registered in the NFIR and the Norwegian Patient Registry (NPR), was also documented.

Paper III

This was a population-based cohort study of women who had already undergone MUS incontinence surgery. Longitudinal data (three data collecting points) prospectively collected by NFIR, and linked with data from MBRN, were used.

3.2 Study populations

An overview of the study populations included in this thesis is provided in **Figure 1**. The women included in Paper I, II, and III were all registered in the nationwide longitudinal cohort of NFIR at the time of study inclusion.

Figure 1: Study populations included in the thesis

In Paper I, a matched cohort of women was identified by linking data from NFIR with data from MBRN, as described in further detail under the Data Processing section. The case group consisted of women registered with one or more childbirths, either vaginal or cesarean delivery, after MUS surgery. In addition, to assess the impact of delivery on continence status, a matched control group of women with no subsequent deliveries after MUS was also included. We aimed to match three controls for every case. The control group was individually matched by year of MUS surgery and had to be within fertile age (<45 years) at the time of surgery. Women in the case group were recruited from the hospital departments reporting to NFIR. In contrast, the women in the control group were, for practical reasons, all recruited from Oslo University Hospital. The inability to consent to study participation due to either reduced mental capacity or lack of language skills in Norwegian or English were the only exclusion criteria. For the complete overview of patient recruitment, see the flowchart of Figure 1 in Paper I.

In Paper II, a random sample of 300 women from NFIR was selected for validation after a sample size calculation, as described in the Sample Size section. Women who had received any form of incontinence surgery for stress- or mixed urinary incontinence (MUI) from 1998 to 2016 and those who had completed a clinical follow-up evaluation at the hospital 6 to 12-months after the surgery were eligible for study inclusion. Most departments routinely invite the women to a clinical follow-up 6 to 12-months after the surgery, which includes filling in a validated questionnaire for symptom score, clinical examination, and urodynamic evaluations, including measuring post-void residuals and performing uroflowmetry. However, for those women who live far from the operating hospital or for other reasons are unable to attend, the questionnaire is filled in during a telephone interview or is sent by post to be filled in by the patient and returned so that the Registry at least receives

subjective postoperative data from these women. In the present study, we wanted to validate subjective postoperative variables and objective postoperative variables often used in research (such as the results from the postoperative cough-jump stress test, post-void residuals, and maximum flow rates). This required that the women also had attended a physical follow-up after 6 to 12 months. To be able to do so, we had to narrow down the population eligible for randomization to women having completed a physical 6 to 12 months exam, thereby excluding women who had no objective follow-up or only subjective data provided by completing the questionnaire.

In Paper III, a complete cohort of women registered in NFIR at the time of study start and those who had undergone their primary MUS surgery for SUI or MUI from 1998 (inception) to 2015 were included. Approximately 70 % of incontinence surgeries performed in Norway were registered in NFIR during this period. To estimate the impact of previous obstetrical history on surgical outcomes after MUS, data from NFIR were merged with data from MBRN, as described in the Data processing section. Women who had not completed a 6 to 12-months follow-up (of any type) or had concomitant pelvic organ prolapse (POP) surgery were excluded. In addition, women > 67 years (born before 1949) were excluded from the study as these could theoretically have given birth to non-registered children before the inception of the MBRN and thereby be falsely classified as nulliparous in the study population. For the complete overview of patient inclusion, see the flowchart of Figure 1 in Paper III.

3.3 Data sources

Norwegian Female Incontinence Registry

Detailed information on NFIR is given in the Introduction chapter. Data from NFIR were extracted and used in all three Papers included in this thesis. Only

data collected pre-operatively, at surgery, and at follow-up 6 to 12-months after surgery were extracted. Long-term data (three years) were lacking for a substantial number of the women included in the Registry, as follow-ups after the first postoperative year are optional for the reporting hospitals. Consequently, these long-term data were omitted as they were deemed to have a high risk of selection bias. Due to the setup of the National Registry, more elaborated on in the introduction chapter, only the department that performed the operation had access to the coded identity lists, making it possible to retrace the patient's identity. Furthermore, the patient's ID was privileged to the local hospital's health care provider until the patient consented to release this information to the study group. Consequently, patient identification for Paper I and the merging of NFIR and MBRN data used for Paper I and III had to be done locally at each reporting department. Further details are given in the Data processing section.

The Medical Birth Registry of Norway

The Medical Birth Registry of Norway (MBRN) is a central health registry established in 1967, covering all deliveries by mandatory notification. It also includes information on maternal health as well as prenatal, obstetrical, and neonatal data. All data in the MBRN are stored in an identified form using the unique national identification number (N-Id), facilitating linkage between registries. Data from MBRN were used to identify women who had given birth after MUS surgery in Paper I, as outlined in the Data processing section. Merged data from the NFIR and the MBRN was used for both Paper I and Paper III. The merged data for Paper I were only released upon return of a signed consent form. For Paper III, only anonymous data were used. For more details on the process of merging data for Paper I and Paper III, see the Data processing section.

The National Patient Registry

The National Patient Registry (NPR) was established in 1997 as a centralized administrative health registry for all Norwegian public hospitals. It also includes private hospitals with public reimbursement contracts. The Registry contains health-related data such as diagnoses and codes for surgical procedures, dates of admission and discharge, and codes for diagnostic and therapeutic procedures by mandatory notification from the hospitals. Since 2008, NPR data are stored in an identified form using N-Id, facilitating linkage between registries. Before 2008, data were reported to the NPR as anonymous data. In Paper II, data from NPR were used to document the completeness of NFIR.

Medical records

In Paper II, a comprehensive medical record review was performed at the woman's local hospital department to assess the accuracy of ten selected key variables in NFIR using the medical records as the gold standard measure. All reviewers were unaware of what had previously been reported to and stored in the National Registry (NFIR). In Paper I, medical records were reviewed if the women in the case group reported any complications after MUS surgery or possible complications related to pregnancy and delivery.

3.4 Patient evaluation tools:

Questionnaires

A validated short-form urinary incontinence disease-specific questionnaire is used by all hospital departments reporting to NFIR [140]. The questionnaire is validated in Norwegian. An English version of the questionnaire is provided in **Appendix 1**. Subjective data on the type of incontinence, the severity of symptoms, and quality of life are collected pre-operatively and at follow-up consultations 6 to 12-months and 3-years after surgery. After completing the

questionnaire, symptom index scores for stress- and urgency incontinence are calculated [140]. The stress and urgency urinary incontinence indices are derived from two domains of clustered questions and range from 0 to 12 (stress) and 0 to 8 (urgency), respectively. A high index score indicates a high symptom load, and 0 indicates no symptoms. These questionnaires were used for subjective data in Paper I and Paper III. For Paper I, the same questionnaire was extended with additional questions on height, current weight, smoking status, parity, mode of delivery before/after MUS, repeat operations for SUI, use of anticholinergics or beta₃-agonists, and any hysterectomies or pelvic organ prolapse surgeries after MUS (**Appendix 2 and 3**).

Cough-jump pad-weighing stress test

Stress urinary incontinence is clinically diagnosed with a stress urinary provocation test in which the weight increase of a pad is measured after the woman performs 20 jumping jacks on the spot and three forceful coughs in the standing position with 300 ml NaCl installed in the bladder [142]. Most departments perform the cough-jump pad-weighing stress test pre-operatively and at the follow-up consultation 6 to 12-months after surgery. The test does not require special equipment, is easy to perform, and has proven reliable at detecting stress incontinence [142].

3.5 Outcome measures

Paper I

The two primary outcomes measured in Paper I were the current subjective SUI cure rate and any change in subjective SUI cure rate from the 6 to 12-months follow-up evaluation after surgery to study participation. *Subjective SUI cure rate* was defined as having a stress urinary incontinence index score of 0, indicating no SUI-related symptoms. The calculation of the stress- and urgency indices is described in the Data sources section. Secondary outcomes

were the rate of repeat operations for SUI, persistent or de novo urgency urinary incontinence, and treatment satisfaction rate. *Persistent or de novo urgency* urinary incontinence was defined as having an urgency urinary incontinence index score ≥ 1 . The *treatment satisfaction rate* was calculated from a single question in the short-form urinary incontinence disease-specific questionnaire. It was defined as the percentage of women stating that they were "*very satisfied*" with the MUS operation when given the choices "*very satisfied*", "*moderately satisfied*", "*neither satisfied nor dissatisfied*", "*moderately dissatisfied*", or "*very dissatisfied*". Additional outcomes were MUS-related complications during or following surgery, injury from the sling during pregnancy and delivery, and voiding dysfunction during pregnancy, delivery, and postpartum.

Paper II

The variables chosen for validation in Paper II were all variables reported on since the inception of NFIR. These variables were collected either before surgery during the patient's initial evaluation, during surgery, or at the physical 6 to 12 months follow-up. They were all considered clinically important and are often a part of the clinical notes in the patients' medical records in addition to the scanned questionnaire. Furthermore, these variables have frequently been used in research projects based on NFIR data [143–150].

The ten variables were as follows:

- Date of surgery
- Preoperative cough-jump stress test (g)
- Preoperative post-void residual urine (ml)
- Preoperative maximum urinary flow rate (ml/s)
- Type of SUI surgery performed
- Complications dichotomized into yes or no (see supplemental **Appendix 1** for a complete list of complications reported to NFIR)
- Postoperative (6 to 12-months) cough-jump pad-weighting stress test (g)
- Postoperative (6 to 12-months) post-void residual urine (ml)
- Postoperative (6 to 12-months) maximum flow rate (ml/s)
- Treatment satisfaction (6 to 12-months postoperatively)

The observed variable agreement between NFIR and the patients' medical records was reported in terms of observed agreement (percentage), chance-corrected proportional agreement (Cohen's kappa), and by calculating the Intraclass Correlation Coefficient (ICC) as described in the Statistical analysis section.

Paper III

Short-term subjective and objective SUI failure rates were Paper III's primary outcomes. *Subjective failure rate* was defined as the percentage of women with a stress urinary incontinence index score > 0 at the 6 to 12-months follow-up evaluation after MUS surgery. *Objective failure rate* was defined as the percentage of women with an increase in pad weight ≥ 1 gram during a standardized cough-jumping pad-weighing stress test. In addition, women included in the study registered as having had a repeat MUS operation were defined as both subjective and objective failures in the analyses.

3.6 Data Processing

Paper I

For the case group:

The collecting and merging of data are illustrated in **Figure 2** and corresponding actions numbers 1 – 10.

1. Information about the study was sent to each participating hospital department reporting to the Norwegian Female Incontinence Registry (NFIR).
2. At each participating hospital department, women operated with any type of MUS at an age less than 45 years were extracted from the local NFIR database. An encrypted data file was generated from each reporting hospital and sent to the Medical Birth Registry of Norway (MBRN) to identify possible study participants (cases). The data file generated included the national identification number (N-Id), a generated study identification number (S-Id), and the operation date for every woman extracted.

3. A de-identified encrypted data file (including only S-Ids) containing a list of identified cases was returned to the respective hospitals from the MBRN.
4. At each hospital, a study information letter, including a consent form and a prepaid reply envelope, was sent to the women identified as giving birth after MUS. If the woman did not return the consent form within four weeks, a nurse or doctor working at the reporting hospital would call the woman giving further information about the study and possibly retrieve confirmation for study participation.
5. Participating cases were asked to sign a study consent form and return it to the local hospital, where they allowed the study doctor to access their identity, telephone number, previously stored data from NFIR and MBRN.
6. Each hospital made a list of received consent forms from the cases that consented to study participation. An encrypted data file was then sent to:
 - a. The research group (including S-Ids, telephone numbers, and the names of consenting women)
 - b. The national NFIR (including S-Ids and local NFIR-numbers)
7. The study doctor performed telephone interviews for all women participating in the study.
8. After the telephone interviews were completed, the study doctor made a list of women who consented to study participation (identified by their S-Ids).

- a. This list was then sent to the Medical Birth Registry of Norway. The previously generated database (containing N-Id, S-Id for all identified women) was reduced to only include participating women (cases). Study identification numbers and delivery data from the study participants extracted from MBRN (in steps 2 – 3, but not released before patient consent) were then sent to the study group for merging with stored data from the national NFIR after step 8b.
 - b. Data from the questionnaires used during the telephone interviews were stored in a research database at a designated secure research server. Identifiable data (name and telephone number) were deleted. A confirmation letter was then sent to the MBRN and national NFIR before patient data were released to the study group.
9. Data from MBRN and NFIR were merged (by using S-Ids). The final analytical database contained only de-identified data.
 10. After quality assessment of the data and after the study was completed, the list at the national NFIR containing both the S-Ids and NFIR numbers was deleted, resulting in an anonymous database.

Figure 2: Data processing for the case group – Paper I

For the control group:

The collecting and merging of data are illustrated in **Figure 3** and corresponding action numbers 1 – 6.

1. Information about the study was sent to Oslo University Hospital, Ullevål.
2. A matched control group of women who had undergone MUS but with no subsequent deliveries was identified in the local NFIR-database (case-to-control ratio 1:3, matched on time of surgery and age < 45 years).
3. A study information letter was sent from Oslo University Hospital to every woman identified, including a consent form and a prepaid reply envelope. If the woman did not return the consent form within four weeks, the study doctor, also working at the hospital, would call the woman for further information about the study and possible confirmation of study participation.
4. The study doctor interviewed the women participating as a control group in the study.
5. Data from the questionnaires used during the telephone interviews were combined with extracted data from the local NFIR database and stored in the research database at a designated secure research server.
6. After quality assessment of the data and after the study was completed, the list at the national NFIR containing both the S-Ids and NFIR numbers was deleted, resulting in an anonymous database.

Figure 3: Data processing for the control group – Paper I

Paper II

The process of collecting data for Paper II is illustrated in **Figure 4** and corresponding actions numbers 1 – 5.

1. Information about the study was sent to each participating hospital department reporting to the NFIR.
2. A total of 300 women were randomly selected from the national NFIR database for study inclusion and data validation. A list containing the unique local NFIR identification numbers was sent from the national NFIR to each contributing hospital department for patient identification.
3. The local gynecologist surgeon or a specially trained nurse was then asked to systematically review the patients' medical records and retrieve information on the ten selected key variables. All reviewers were blinded to what was previously reported to and stored in the National Registry.
4. The retrieved data on the selected variables were then sent back to the national NFIR and combined with data previously stored in the database.
5. An anonymous database containing the coupled data from the national NFIR database and retrieved data from the patients' medical records were given to the study group for comparison and data analysis.

Figure 4: Data processing – Paper II

Paper III

The collecting and merging of data are illustrated in

Figure 5 and corresponding action numbers 1 to 5.

1. Information about the study was sent to each participating hospital department reporting to the NFIR.
2. Patients operated on with any type of MUS were extracted from the local NFIR database at each participating hospital department.
 - a. An encrypted data file was sent to the Medical Birth Registry of Norway (MBRN) to identify possible study participants (cases). The data file generated included the national identification number (N-Id), a generated study identification number (S-Id), and the operation date for every woman extracted.
 - b. A data file containing the study identification numbers (S-Id) for each identified woman was at the same time sent to the national NFIR
3. MBRN deleted the connection between N-Id and S-Id before:
 - a. Sending the national NFIR a data file containing a list of women that were identified in the MBRN database (containing S-Ids, but no other patient ID)
 - b. Releasing MBRN data to the study group (containing S-Ids, but no other patient ID)
4. The national NFIR deleted the connection between S-Id and the NFIR identification number before releasing NFIR data to the study group (containing S-Ids, but no other patient ID).
5. The study group merged the data from MBRN and NFIR to a true anonymous database stored on a designated secure research server.

Figure 5: Data processing – Paper III

3.7 Sample size

As prevalence data for childbirths after MUS surgeries were lacking, the number of patients required for robust statistical analysis in Paper I was not possible to calculate. Furthermore, the long-term impact of childbirths after MUS remained unknown. The study group thus aimed to include all women identified as giving birth after MUS operations in Norway.

For Paper II, the number of women required for statistical analysis was determined by sample size calculation for Cohen's kappa and a statistician's recommendation. Sample size calculation was performed with a power of 80 % and a significance level of 0.05. Thus, a sample size of 221 was required to test for a statistically significant difference between substantial (0.80) and excellent (0.90) chance-corrected proportional agreement.

No sample size calculations were performed for Paper III. This study was based on a large unselected population, including all women registered in NFIR from 1998 to 2016 and those who had completed incontinence surgery and 6 to 12-months follow-up evaluation ($n = 14,787$). Consequently, we considered the sample size to represent the whole population of women undergoing SUI surgery in Norway adequately.

3.8 Statistical analysis

Continuous variables are presented as medians with range or interquartile range, and dichotomous variables are presented as frequencies (percentages). Most of our data sets were not normally distributed and did not meet the assumptions for parametric tests. Therefore, the Mann-Whitney test was used when comparing continuous variables between groups. Dichotomous variables were compared using Fisher's exact test. McNemar's test was used on repeated nominal data measurements.

Multivariate logistic regression analysis was applied to evaluate potential risk factors for subjective failure (Paper I and Paper III) and objective failure (Paper III). Independent variables with a significance level of 0.20 in the univariate analysis were included in the multivariate regression model. A backward variable selection was then made by stepwise removal of variables with significance levels > 0.05 . Included variables in the multivariate model were checked for any potential interaction. The final model was tested using a goodness-of-fit test (Hosmer-Lemeshow).

In Paper II, inter-rater agreement for categorical data was presented in terms of observed agreement (percentage) and chance-corrected proportional agreement (Cohen's kappa) with a 95 % confidence interval (CI). When assessing the accuracy for ordinal variables, the quadratic weighted kappa was used. Cases with missing variables were excluded. Intraclass Correlation Coefficients (ICC) were calculated for continuous variables to assess the consistency of measurements made by different observers for the same variable. ICC was calculated using a one-way random-effects ANOVA model, yielding a correlation value between 0 and 1, with values closer to 1 representing stronger reliability. Furthermore, to show the disagreement's magnitude, we calculated the mean differences between the raters with a 95 % confidence interval. When interpreting Cohen's kappa and ICC, we used the following quality terms suggested by Landis and Koch [151]: Slight agreement 0 - 0.20, fair agreement 0.21 - 0.40, moderate agreement 0.41 - 0.60, substantial agreement 0.61 - 0.80, and excellent agreement > 0.80 .

Linear regression analysis was performed to explore if accuracy for the selected variables changed over time or were related to operative volume at the reporting hospital departments (Paper II). The measured differences between medical records and the Registry values for continuous variables were used as the regression model's dependent variables. The independent

variable used was years since surgery and high-volume vs. low-volume departments. High-volume departments were defined as the five hospitals that perform the highest number of annual incontinence surgeries (>150).

We used different strategies for dealing with missing data:

In Paper II, some of the variables selected for validation had a high degree of missing values. To ensure that the missing values were not an indication of inadequate reporting to the Registry, we compared the distribution of missing data in the Registry to the patients' medical records.

In Paper III, we only included variables with data missing in < 20 % of the participants in the logistic regression analysis. Logistic regression was used to examine whether any of the variables chosen predicted missingness to conclude whether data were missing-completely-at-random or missing-not-at-random. The final analyses were restricted to individuals with complete data on the variable required for a specific analysis.

Sensitivity analyses were performed to explore potential selection bias:

In Paper I, short-term objective and subjective outcomes extracted from NFIR were compared for responders and non-responders in the study group.

To determine whether the women chosen for validation in Paper II were representative of the entire cohort, baseline characteristics and stored values for the selected continuous variables were compared between the women randomized for validation and the total Registry population.

The various statistical analyses were performed using Statistical Package for the Social Sciences version 23.0 (IBM SPSS), or STATA: Software for Statistics and Data Science version 16.0 (StataCorp).

3.9 Ethics and formal approvals

Ethical approval for all studies included in this thesis was obtained from the Regional Committee for Medical and Health Research Ethics (REC) for South-East Norway (#2015/434) and the local Data Protection Officer at Oslo University Hospital. Furthermore, the principles for medical research involving human subjects were followed in line with the Declaration of Helsinki [152].

For Paper I, women were contacted and given information about the study by health personnel (doctor/nurse) at their local hospital where the MUS surgery was performed. The patient IDs were privileged only to the local hospital's personnel until the patients consented to this information (in a de-identified form) being released to the study group. Written informed consent was received for all women included in the study. If the woman included in the study reported SUI recurrence or other bothers related to the MUS surgery, the women were offered a follow-up consultation at their local hospital department.

Written patient consent was not deemed necessary by the study group for Paper II. The study represented a clinical audit of treatment given and would contribute to quality control for internal hospital use. REC was nevertheless consulted and approved the omission of patient consent.

Exemption to patient consent requirement was also given for Paper III (by REC) due to no foreseeable risk of violating personal data and the need for completeness of data for study validity. Only an anonymous file was released to the study doctors. The high number of women included and the nature of the variables used made any indirect identification of participating women impossible. Furthermore, the study group argued to REC that it was unlikely that contacting all women operated for MUS in the NFIR registry would result

in a reasonable response rate. Self-selection bias and low participation rates would potentially reduce the study's validity and, consequently, its clinical usefulness for future female urinary incontinence populations. Therefore, total confidentiality for the included women was maintained in the final study file, as shown in the Data processing section.

4 SUMMARY OF RESULTS

4.1 The impact of childbirth after mid-urethral sling surgery

In Paper I, the impact of pregnancies and deliveries after MUS surgeries on the long-term subjective incontinence outcome was investigated. As women are advised to postpone MUS surgery until completion of childbearing, these women are few and dispersed across the country. Consequently, we had to use the combined data from the Medical Birth Registry of Norway and NFIR to identify eligible study participants. We identified 87 women, of which we managed to include 72. These 72 women, with one or more deliveries after MUS, constituted the case group in our cohort study. In addition, a matched control group of 156 women (1:3 ratio) without subsequent childbirths after MUS was located through the NFIR. For the matching process and criteria, see the Method chapter of the thesis.

The median follow-up time for the whole study group (cases and controls) was ten years. A detailed comparison of subjective surgical outcomes between cases and controls is presented in Table 2 in Paper I. The main finding was that there did not seem to be any significant differences in patient-reported SUI cure rates between women with and without childbirths after MUS (82 % vs. 75 %, $p = 0.31$). Furthermore, there did not seem to be any difference in long-term patient satisfaction rates or long-term urgency urinary incontinence symptom bother. Please see the Methods chapter of the thesis for the definition of treatment satisfaction rates and urgency urinary incontinence symptom load.

Only a few women in the case group had more than one childbirth after MUS ($n = 12$), but we found that these had a significantly lower cure rate (50 % vs. 88 %, $p = 0.006$) than women who had only one childbirth after MUS.

However, the low case number implies that this result must be interpreted with caution. Furthermore, we found no significant differences in SUI cure rates between women who had vaginal deliveries and those with cesarean deliveries after MUS in the case group (77 %vs. 88 %, $p = 0.36$). Again, the number of patients is low, and the results must be interpreted with caution.

We also performed a logistic regression analysis with delivery after MUS as the variable of interest and recurrence of subjective SUI being the dependent outcome variable to adjust for potential confounders. The other variables tested in the model were BMI, parity before MUS, repeat operation for SUI, smoking, hysterectomy after MUS, pelvic organ prolapse surgery after MUS, and age at the time of MUS. Delivery after MUS was not found to be an independent risk factor neither in the univariate or the multivariate analysis (aOR 0.8, 95 % CI 0.3 - 1.7).

Three women in the case group reported possible sling-related complications during pregnancy, these were recurrent urinary tract infections ($n = 2$), and the need to perform clean intermittent catheterization ($n = 1$). However, no other significant complications related to the MUS during pregnancy and delivery were reported.

4.2 The reliability and completeness of NFIR

As detailed in the Methods chapter, we randomly extracted 300 women from the Norwegian Female Incontinence Registry from its inception until 2017 who had undergone stress incontinence surgery and had completed a physical follow-up consultation 6 to 12-months after the surgery. The randomization procedure included patients from 27 hospitals. As six hospitals declined to validate their randomized assigned patients, the included patient number was reduced to 285. The results from this validation process were published in Paper II.

We found that the inter-rater agreement for categorical variables, expressed as kappa values, and intraclass correlation coefficient (ICC) for continuous variables to be excellent. The kappa and ICC values were both > 0.80 for all the selected variables. Table 2 and Table 3 in Paper II present the specific kappa and ICC values for each of the ten key variables. The agreement was 96.8 % between NFIR and the source data (the patients' medical records at the reporting hospitals) for the type of surgery (kappa 0.93, 95 % CI 0.88 - 0.98). Nine women (3.2 %) had an incorrect type of surgery registered at NFIR. Inter-rater reliability for complications occurring during or immediately after the surgery was slightly lower (kappa 0.86, 95 % CI 0.71 - 1.00), but the overall agreement between NFIR and the medical records concerning complications was high (98.9 %). Two women with complications were reported to NFIR but not listed in the patients' medical records, and one woman with a complication had not been reported to the Registry. We found excellent agreement (ICC 0.94 - 1.00) for all continuous variables chosen for validation, supporting strong reliability of NFIR when using the medical records as the gold standard measure (source data). However, a substantial number of missing values were found in NFIR for both the pre- and postoperative maximum urinary flow rates (28.1 % and 35.8 %) and the postoperative cough-jump pad stress test (11.9 %).

The validation process revealed that the accuracy of the ten key variables chosen for validation did not change significantly over time. Furthermore, we could not demonstrate any association between accuracy and annual surgical volume comparing high- versus low-volume hospitals.

From 2008 to 2017, the completeness of NFIR increased from 61 % to 99 % for the hospitals reporting to the registry. From the inception of NFIR in 1998 until 2017, the coverage improved from 23 reporting hospitals to include all

38 public hospitals and one private hospital performing incontinence surgery in Norway.

4.3 The impact of childbirth before mid-urethral sling surgery

After establishing the NFIR as a reliable research tool, we moved on to this thesis's third (and last) specific aim: to investigate any potential impact of previous obstetrical history on the short-term (6 to 12-months) subjective and objective failure rates after primary MUS surgery. Again, as we did for Paper I, we had to merge data from NFIR with data stored at the MBRN. Please see the Data processing section under the Methods chapter of the thesis for details about the merging process. The results from this part of the thesis were published in Paper III.

A cohort of 23,421 women was located through the NFIR, and 14,787 were eligible for study inclusion. These women had all been operated for SUI with some form of MUS from 1998 to 2016. Baseline clinical characteristics, type of surgery, and short-term failure rates are presented in Paper III (Table 1). We found that subjective and objective short-term failure rates were 28.9 % and 7.7 % for the total study population. When comparing nulliparous women with parous women, nulliparous had a significantly worse outcome with subjective failure in 33.8 % vs 28.7 %, $p = 0.010$ and objective failure in 10.3 % vs 7.6 %, $p = 0.036$. However, we found that nulliparous women, when compared with parous women, were significantly older ($p < 0.001$), had a higher BMI ($p < 0.001$), and had a higher preoperative symptom load for both stress and urgency urinary incontinence, as indicated by their higher preoperative stress and urgency urinary incontinence symptom scores ($p < 0.001$).

The significant differences observed for the constitutional factors could theoretically be explanatory confounders for the short-term outcomes.

Consequently, we build a logistic regression model to adjust for these possible confounders. The potential risk factors for subjective and objective failures and the resulting unadjusted and adjusted odds ratios (aOR) are presented in Paper III (Table 2 and Table 3). Being nulliparous seemed to moderately increase the rates of subjective and objective failure in the univariate analysis (OR 1.27 (95 % CI 1.05 - 1.53), $p = 0.012$, and 1.41 (95 % CI 1.02 - 1.95), $p = 0.037$). Other variables appearing as risk factors in the univariate analysis were head circumference (subjective failure), age at first delivery (objective failure), and time from last delivery until surgery (objective failure). However, after adjusting for the confounding constitutional factors included in the multivariate analysis, being nulliparous was still the only obstetrical factor significantly impacting short-term objective failure after MUS (aOR 1.60, 95 % CI 1.07 - 2.40, $p = 0.022$). None of the obstetrical factors tested in the multivariate regression analysis were significantly associated with subjective failure. BMI at time of surgery, degree of leakage before surgery (preoperative cough-jump pad-weighing stress test results), degree of preoperative stress- and urgency symptom loads (expressed as preoperative stress- and urgency urinary incontinence index scores), preoperative maximum urinary flow rate less than 15 ml/s, type of sling utilized, and surgical complications were all risk factors associated with subjective and/or objective failure rate in the adjusted regression analyses.

5 DISCUSSION

5.1 Discussion of methodology

5.1.1 Study design and population

All three studies included in this thesis were based on data from the nationwide prospective longitudinal cohort of women included in the Norwegian Female Incontinence Registry.

In Paper I, a matched cohort study design was selected to evaluate the impact of pregnancy on continence status for women previously operated with MUS. Matching is a strategy to reduce the potential effect of confounding factors in a study design [153]. In matched cohort studies, the exposed individual is compared with one or more unexposed individuals. The matching criteria are usually on one or more potential confounding factors [154]. Suppose each exposed individual is perfectly matched with an unexposed individual, and there is no loss to follow-up or missing data. In that case, the matching procedure results in equal distribution among both groups, eliminating confounding by the matching variable [155].

In Paper III, a cohort study design with longitudinal data (recorded pre-operatively, per-operatively, and 6 to 12 months post-operatively) from the surgical cohort of women already included in the Norwegian Female Incontinence Registry (NFIR) was selected. Data from NFIR were then merged with data from the Medical Birth Registry of Norway (MBRN). Since the aim was to explore if the same obstetrical factors that are assumed to be significant risk factors for the development of SUI also could play a role in the outcome of the surgery, the population included in the study represented a selected group of women already having developed SUI of such magnitude that surgery was warranted and performed. The impact of previous

obstetrical factors on the general risk of developing SUI was not assessed. This would have required the inclusion of a cohort of women not surgically treated for their SUI and a different study design.

5.1.2 Internal validity

Internal validity refers to the extent to which an association identified in a study cannot be explained by other factors [154]. To draw a reliable conclusion in observational studies, other causal explanations have to be excluded. Random error is related to the precision of establishing a causal relationship between a given exposure and disease and can be reduced by increasing the sample size [154]. Systematic error is related to the study's validity and is not affected by increasing the sample size [154]. The validity can be reduced by error related to the recruitment of study participants (selection bias), factors that influence both the supposed cause and the supposed effect (confounder), or systematic distortion when collecting information on exposures and outcomes (information bias) [153, 154, 156]. Considerations of random and systematic error are inapplicable for Paper II, as this was a validation study, and are only applicable for Paper I and Paper III.

5.1.2.1 Precision

Paper I and -III were based on data from a nationwide longitudinal cohort of the Norwegian Female Incontinence Registry (NFIR) with proven high data reliability [141]. The population examined in Paper I was relatively small and might represent an underpowered study. It was not possible to calculate the sample size required for robust statistical analysis, as prevalence data for childbirths after MUS surgeries were lacking. When interpreting the results, such errors must be taken into account. However, similar results were found for comparable populations in both a Swedish and a Finnish study recently

published [157, 158], indicating that the results probably represent the group examined and that the risk of type II error is low.

The precision for the study presented in Paper III is regarded as high due to the large sample size and narrow confidence intervals (CI). The precision level became somewhat lower when adjusting for possible confounders, as the sample size was reduced by 31 % due to missing variables. However, the CI remained narrow, and secondary regression analysis using multiple imputations for missing variables, as described further on, did not significantly alter the results.

5.1.2.2 Selection bias

Selection bias may occur when the exposure-outcome relationship varies between the study population and those potentially qualified for study inclusion [154, 156]. The women included in Paper I and III were all selected from a large nationwide population-based registry with proven high coverage and variable completeness [141], minimizing the bias on how a participant is identified and potentially included in a study. The response rate could introduce some degree of selection bias. Response rates between 60 % and 80 % are usually considered acceptable [159], but Morton and co-workers have also demonstrated that the response rate not always necessarily is correlated to validity [160].

In Paper I, the response rate was 83 % for the case group and 72 % for the control group. The women included in the study were not given any compensation. Still, participants that reported SUI recurrence or other bothers related to the MUS surgery were offered a follow-up consultation at their local hospital department. The control group had a significantly lower SUI cure rate than the case group at short-term evaluation (6 to 12 months). Theoretically, responders could have more symptoms than non-responders.

Hence a self-selection bias could have been introduced. Therefore, a non-responder analysis was performed comparing baseline demographic characteristics and the 6 to 12-months follow-up outcomes (obtained from NFIR) between the responders and non-responders. This sensitivity analysis revealed no evidence that a selection bias had been introduced, as both groups were found similar for the tested outcomes.

Missing data is a common problem in observational studies and might reduce the sample size available for analysis and introduce selection bias [161]. There is no established cut-off regarding an acceptable proportion of missing data on important variables in a data set, but 10 % to 20 % is usually considered acceptable, while higher ratios might introduce bias [162]. In Paper III, some of the possible confounding factors included in the regression analysis had a substantial proportion of missing values. Information on BMI at the time of surgery was missing for 23 % of the women when assessing the risk for subjective and objective failure after MUS as this variable was included in the NFIR as late as 2004. Urodynamic variables were initially not included in the analysis due to many missing entries (as shown in Paper II). However, after a request from the reviewers of Paper III, preoperative post-void residual urine and preoperative maximum urinary flow were included in the regression model. Measurement of maximum urethra closure pressure (MUCP) was missing for over 60 % of the women included in the data set. We therefore chose to omit MUCP from the final analysis. This test is not performed at all departments and would result in an unacceptably high degree of missing observation in the final analysis. After including all possible confounding factors identified in the univariate model, only 69 % of the study participants were included in the final multivariate regression analysis.

There are different statistical methods for analyzing data sets with missing data, such as multiple imputations and inverse probability weighting [162–

164]. However, the most common approach is a complete case analysis, in which participants with missing data are excluded from the study.

It has been suggested that missing data mechanisms have a more significant impact on research findings than missing data proportions [164].

Furthermore, Bartlett et al. have demonstrated that a complete case analysis using multivariate logistic regression can produce unbiased estimates of associations under a wide range of missing data mechanisms in large samples [165]. In Paper III, analysis of missing-mechanism revealed that the missingness of BMI was related to age at operation and type of MUS, indicating that BMI was missing not at random (MNAR) rather than missing at random (MAR) or missing completely at random (MCAR). However, the missingness of BMI was not associated with the outcome (objective or subjective MUS failure). According to Bartlett et al., a complete case logistic regression analysis is valid if the missingness is dependent on covariates (confounder, exposure, or both) but not the outcome [165]. Additional analysis with multiple imputations of missing values was therefore also performed. Multiple imputations is a statistical procedure where missing data are replaced by estimates of plausible values for missing data, creating "complete" data sets. Multiple imputations can be used if the missingness mechanism satisfies the MAR assumption [163, 164]. However, using imputed data in the multivariate logistic regression analysis in Paper III did not change the results, indicating that the regression analysis estimates were unbiased.

5.1.2.3 Confounding

Confounding is a factor that exerts an effect on both the dependent and the independent variable, causing a false association [153, 154]. Strategies to reduce the risk of confounding in a clinical study include matching, stratification, and adjusting for confounding in regression analysis [153].

In Paper I, we found that the case group (exposed) had a significantly higher SUI cure rate than the control group at the short-term evaluation (6 to 12 months). The exposed women (pregnancy after MUS) were matched with three unexposed women (no pregnancy after MUS) from the same population (NFIR). The women's age at MUS and equal follow-up time after MUS were initially selected as matching factors. Recruitment of women to the control group was done at Oslo University hospital for pragmatic reasons. However, identifying sufficient numbers of fully age-matched women (± 2 two years) from one hospital proved challenging. Consequently, the matching criteria had to be changed, of which follow-up time after MUS was decided on as the most critical matching criterion. The additional adjusted matching criterion was that all women in the control group had to be within fertile age (<45 years) at the time of surgery. Despite the effort to match the two groups, the control group was significantly older and had a higher parity than the case group at the time of their primary MUS. Aging and increased parity are associated with increased SUI risk and could potentially explain the higher SUI cure rates observed in the case group [3, 12].

A logistic regression analysis was performed to explore the possibility of confounding from age at the time of surgery and parity due to poor matching. This revealed that parity, but not age, was a significant risk factor in the univariate regression analysis. However, after adjusting for parity in the multivariate analysis, childbirth after MUS surgery was still not an independent risk factor for SUI recurrence. Surprisingly, having two or more children before MUS surgery seemed to reduce the risk of SUI recurrence. When exploring the composition of the control group, we found that three women were nulliparous. When these women were excluded from the regression analysis, the effect of parity was no longer significant. Interestingly, we found the same association between being nulliparous

before MUS and the risk of subjective failure after MUS in Paper III. As hypothesized in Paper III, these women might have a different underlying pathophysiological mechanism for incontinence than urethral hypermobility caused by trauma to the pelvic floor. Therefore, being nulliparous might be considered a confounding factor in Paper I. Ideally, all women in the control group should have been parous women to match the case group (exposed).

In Paper III, logistic regression analysis was also used to account for potential confounding factors. In regression analyses such as these, there are always unknown factors that could play a significant role in confounding mechanisms. As discussed in Paper III, the pathophysiology of SUI in non-parous women is probably caused by other factors than trauma to the pelvic floor. Possible factors hypothesized are different connective tissue composition, a poor sphincter function, or a dysfunctional pelvic floor due to age-related atrophy of muscles or undiagnosed neurological diseases [57, 166]. Studies have demonstrated (conflicting evidence) that women with intrinsic sphincteric deficiency (ISD) have poorer cure rates after TVT than women with urethral hypermobility [83, 148, 167]. Measurements of maximum urethra closure pressure (MUCP) or Valsalva leak point pressure are two methods used to evaluate urethral sphincteric function. MUCP below 20 cm H₂O is considered to indicate urethral dysfunction or ISD [34]. However, MUCP measurement can be challenging to interpret due to significant MUCP variation in both continent and incontinent women and a lack of standardization of testing techniques [34]. Uroflowmetry and urodynamics are part of the standard clinical workup before SUI surgery, and urodynamic data are regularly reported to the Registry when performed. However, these urodynamic evaluations are not mandatory for the reporting departments, although recommended, and some departments do not, therefore routinely perform or report a complete urodynamic examination.

For instance, we found that MUCP was missing for over 60 % of the women included in the analysis for Paper III. Consequently, MUCP was omitted in the multivariate logistic regression analysis, as this would lead to an unacceptably high degree of missing observation in the analysis. In the group of women with complete urodynamic workup, only 1.8 % had an ISD. The non-parous women had a higher, although not significant, prevalence of ISD than parous women (3.1 % vs. 1.8 %), indicating that ISD might be a confounder that should have ideally been included in the multivariate regression analysis.

In Norway, we do not have standardized protocols for when to use what type of mid-urethral slings as they are, by most Norwegian surgeons, regarded as equal when it comes to primary SUI surgery. The choice of tape is therefore exclusively made at each hospital at the surgeon's discretion. However, most departments in Norway use the retropubic MUS (78 %). Therefore, the lack of standardized patient selection protocols might be a confounding factor (confounding by indication) that we could not adjust for in the analysis. The surgeon's experience and a proper selection of patients are also important factors for the outcomes after MUS. Unfortunately, we could not adjust for these variables in the analysis, as data are not registered related to surgery volume experience. However, most surgeons in Norway performing MUS operations are experienced senior consultants in gynecology.

5.1.2.4 Information bias

Information bias is related to inaccurate measurements or misclassification of exposures, variables, or outcomes in a study [154, 156]. Information bias can significantly be reduced by a validation study, in which an investigator compares the accuracy of a measure or data with a gold standard measure [168]. When information is incorrect but consistent across groups, this is referred to as non-differential misclassification. In clinical studies, this could be related to a test's ability to correctly classify individuals as truly

exposed/unexposed for a risk factor or to correctly classify people into truly having the disease or truly not having the disease. Paper I's primary outcome was the current subjective SUI cure rate, defined as having a stress urinary incontinence index of 0. In Paper III, subjective failure was defined as a stress urinary incontinence index score > 0 at the postoperative 6 to 12-month follow-up. The questionnaire used to assess subjective SUI and UUI symptoms is described in further detail in the Methods section. The questionnaire has been validated, indicating high test-retest reliability and internal consistency [140]. However, the correlation to objective tests such as the 24-hour pad test and the cough-jump-pad test was moderate. Currently, no cut-off value has been established when using stress urinary incontinence index scores to classify cure or persistent SUI. The criteria used in Paper I and III might be too strict, possibly introducing a misclassification bias. A sensitivity analysis was performed, where the cut-off value for stress urinary incontinence index score was changed to ≤ 2 . According to that definition, the total population's subjective failure rate in Paper III was reduced from 29 % to 18 %. However, in the univariate and multivariate logistic regression analyses, the associations previously found remained unchanged. Hence, the risk of misclassification bias was considered low.

Differential misclassification occurs when the likelihood of misclassification differs between groups based on exposure or disease [154]. Such misclassifications could be due to vague memory of past exposures (recall bias) or the interviewer's tendency to obtain answers that support preconceived assumptions (interviewer bias). In Paper I, recall bias was considered non-existent as the exposure status (delivery status after MUS) was obtained from Norway's Medical Birth Registry (MBRN), covering all births in Norway by mandatory notification.

5.1.3 External validity

External validity is the ability of a study's conclusion to be generalized to other groups of people or settings [154]. The populations included in this thesis are all sampled from a nationwide registry with proven high data reliability and coverage [141]. The Registry consists of data from a large heterogeneous population, collected from high- to low-volume hospital departments, representing the typical SUI patients in Norway. The Registry provides a good description of the true impact of intervention in actual practice, not only the effect of expert surgeons.

In Paper I, most women in the case group (pregnancy after MUS) had only given birth once, and their results cannot be generalized to women who have had multiple births. In Paper III, we excluded secondary SUI operations, limiting the conclusion to patients undergoing primary MUS only. Women born before 1949 were excluded, as these could theoretically have given birth to non-registered children before the inception of the MBR, thereby limiting the generalization of outcomes to extend also to older women > 67 years. Non-MUS and concomitant POP surgery were also excluded, limiting the generalization of outcomes for these specific groups.

5.1.4 Methodological considerations Paper II

A sample size of 221 cases was required to test for a statistical difference between substantial (0,80) and excellent (0,90) chance-corrected (kappa) proportion agreement. The study aimed to validate not only subjective postoperative variables but also objective postoperative variables (such as postoperative cough-jump pad-weighing stress test results, post-void residual measurements, and maximum flowrates) that required the women to have attended a physical examination. In order to do so, the population eligible for randomization was narrowed down to women that had completed a physical examination at their 6 to 12 months follow-up, thereby excluding women

with no follow-up or only subjective data provided by telephone interview or by having returned the short-form urinary incontinence disease-specific questionnaire by mail.

We included 285 women (of 300 aimed for) from 21 of 27 reporting hospitals (for the period included in the study). The purpose of doing a randomized extraction was to obtain a representative population for validation. To evaluate if there was an unintentional selection bias, a baseline analysis was performed by comparing the selected continuous variables for the women included in the study (n=285) with the total population in the Registry (Table 1, Paper II). The analysis did not reveal any significant differences between the groups, indicating a representative study population with no unintentional selection bias.

Cohen's kappa estimates the inter-rater reliability between two raters for the same variable and is corrected for the eventuality that they might agree by chance. The prevalence of a trait influences the kappa coefficient. If an attribute is skewed, the probability of agreeing by chance will increase, and the precision level will decrease. In the selected population for validation, less than 5 % had a surgical complication, resulting in a strongly skewed trait distribution. Even though the observed agreement between NFIR and the medical record was 98.9 %, the estimate of inter-rater reliability was 0.86 with a wider confidence interval for the kappa coefficient than the other estimates (95 % CI 0.71 - 1.00). In this situation, the likelihood of agreeing by chance is so high that the estimate will inevitably be imprecise. All estimates for agreement for the selected variables, except complications (yes/no), had a narrow 95 % CI indicating a high precision level.

There are several strengths in the study presented in Paper II. The number of cases extracted for validation was well within the estimated sample size

calculations, indicating that the study was well powered to detect robust inter-rater estimates. Furthermore, when assessing the accuracy of the selected variables, the reviewers were blinded to the previously stored information in the National Registry. Finally, the study included women from almost every reporting hospital, minimizing the risk of selection bias.

A limitation of the study was that not all NFIR variables were validated. Despite a high degree of accuracy of the variables selected for validation, one can only assume that the other variables have the same degree of accuracy. Another concern is the possibility of introducing new errors during the re-extraction of data from the patients' medical records. Furthermore, some of the variables selected for validation had a high degree of missing values, such as pre-and post-operatively maximum flow rates and the postoperative cough-jump pad-weighing stress test. A phenomenon known as *respondent fatigue* may occur when requesting excess or irrelevant information, deteriorating the data quality [169]. However, analysis of the mechanism of missingness revealed that the distribution of missing data in the NFIR was similar to the patients' medical records. These findings indicate that the missing values were not due to inadequate reporting to the registry but rather that some departments do not routinely perform a complete urodynamic evaluation.

5.1.5 Questionnaire

All hospital departments reporting to the Norwegian Female Incontinence Registry use the same validated short-form urinary incontinence disease-specific questionnaire [140]. As described in the Methods section, symptom index scores for stress- and urgency urinary incontinence are calculated after completing the questionnaire. Stress urinary incontinence index scores were used as outcome measures for both Paper I and -III, as it provided a coherent definition of subjective stress urinary incontinence. In Paper I, the same

questionnaire was used when performing the telephone interviews of the women included in the study. It allowed for a consistent comparison of individual patient symptom scores to previously recorded symptom scores in the NFIR. All women included in Paper I were interviewed by the same doctor (Dyrkorn). Potential misunderstandings related to the questionnaire were corrected during the interview, increasing the validity of the patient's response.

5.1.6 Ethical Considerations

Before beginning the PhD project, the various ethical aspects of conducting studies that involve the merger of potentially sensitive data from various sources were thoroughly considered and contemplated. Important considerations must always be made to ensure that the use of potentially sensitive registry data does not inadvertently violate the personal integrity of participating women.

The Health Register Act of Norway regulates the use of information in health registries [170]. The purpose is to enable the use of health information to provide sufficient information and knowledge for the health service and health administration to fulfill their tasks of providing safe and effective health care without violating people's privacy. The act also facilitates health information in research and statistics, which provides new information and knowledge. In the preparatory works of the Health Register act, it is emphasized that consideration of the patient's best interests must always be paramount. This signifies that there must be strong arguments to deviate from the requirement for consent and any use of sensitive data for purposes other than individual patient treatment. Possible exceptions to the general rule of consent are when data is given out for research purposes, as well as for monitoring and improving the quality of health care. The assumed societal

benefits and information security of the research project are important premises to consider when evaluating exceptions to consent.

Registry studies, in which data from various health registers are linked, allow for important research on large patient groups, which can lead to significant advances in medical science. One major dilemma is how to determine the balance between societal benefits and privacy. Any disclosure of sensitive data for research purposes involves an intrusion into people's lives and raises the possibility that information can be used in a way that undermines the individual's right to self-determination and integrity. The main rule is that patients must give their permission for their data to be shared with researchers. However, in some cases, obtaining consent from large patient populations may be impossible or highly resource-intensive, resulting in skewed data for the researcher. It can thus be argued that in certain circumstances, circumventing the requirement for consent may be appropriate, as such data can provide more knowledge, better patient treatment, and economic benefit. In such cases, individuals involved in studies must not be harmed as a result of the research. Furthermore, the researchers should be clear about the importance of data access in terms of societal benefits.

The following ethical considerations were made for the three studies forming the basis for this thesis;

In Paper I, written informed consent was obtained from all women who participated in the study. Participants were free to withdraw from the study at any time without affecting their current or future treatment and follow-up. The women did not undergo any physical examinations but were subjected to a structured telephone interview in which potentially sensitive topics such as urinary incontinence and potential pregnancy and birth-related complications

were discussed. However, the women were given medical advice or referred to a urogynecologist at their local hospital as appropriate to their needs.

Exemptions to patient consent requirements were given for Paper II and Paper III by Regional Committee for Medical and Health Research Ethics (REC). Paper II represented an audit of data that the patients had already given their signed consent to be stored in the NFIR and used for quality improvement measures. As long as the women's identity was not revealed to the study doctors, the REC concluded that additional written consent to the one already given was redundant for the audit. Furthermore, no new examinations that could cause physical or emotional harm were performed on the women in the study. Finally, the study's findings were published in a non-identifiable manner.

Stress urinary incontinence (SUI) is a common condition. Childbearing is considered a significant risk factor for the development of SUI. Combining registry data from the Norwegian Female Incontinence Registry (NFIR) and the Medical Birth Registry of Norway (MBRN) enabled us to evaluate the impact of previous obstetrical history on the outcomes of mid-urethral sling (MUS) surgery. Even though having urinary incontinence is not life-threatening, it gravely diminishes the quality of life for many women worldwide. Therefore, it is essential to gather as much knowledge as possible on any potential effects of obstetric factors on the outcomes of surgery for SUI. In this way, optimal preoperative counseling and realistic expectations regarding surgery outcomes can be given for the many women contemplating this type of surgery. For Paper III, only anonymous data were given to the study doctors as elaborated under Data Processing in the Methods section of the thesis. None of the women included in the study underwent new examinations that could cause physical or emotional harm. Also, total confidentiality was maintained for all women included in the study, as

outlined in the Methods section. Hence, combining data from NFIR and MBRN without patient consent was thought to be ethically justifiable.

We therefore concluded in the planning that the project in full was ethically well justified and in accordance with the Helsinki Declaration [152]. Our consultation with the Regional Committee for Medical and Health Research Ethics (REC) for South-East Norway and the approval given by the local Data Protection Officer at Oslo University Hospital support this view. As quality assurance control is an important mandatory requirement for all hospitals in Norway, it could be argued that not performing studies like the present PhD thesis would not be in line with optimal research ethics and patient-centered care.

5.2 Discussion of results

5.2.1 The impact of pregnancy after mid-urethral sling surgery

In Paper I, the main finding was that long-term outcomes in women who gave birth after mid-urethral sling (MUS) surgery were reassuring and comparable to women with no deliveries after MUS. Recurrence of SUI symptoms was not associated with the mode of delivery, but women with more than one delivery after MUS were more likely to experience treatment failure.

Before the present study, data on the impact of pregnancy and delivery after MUS were limited to small cohort studies and case reports with methodological limitations [94, 95, 97, 171]. In 2015, Cavkaytar et al. published a case series and comprehensive review of 15 case report publications, including 54 women with childbirths after MUS [96]. Using logistic regression on the pooled data from women with childbirths after MUS, the author evaluated potential risk factors for postpartum SUI. Only incontinence during pregnancy in these women with pregnancies after MUS was found to be a risk factor for SUI. Delivery mode, parity, age, type of MUS

did not seem to be risk factors for the recurrence of SUI symptoms. Adams-Piper et al. published in 2016 the results from a cohort study including 26 women [172]. It was the most extensive single case series, at that time, of women with subsequent deliveries after MUS, and it included follow-up after 11 vaginal deliveries and 15 cesarean sections. They observed no MUS-related complications, but one patient developed recurrent SUI postpartum followed by a second MUS operation.

In 2018, just before completing the study presented as Paper 1 in this PhD-thesis, a Swedish research group published a large matched cohort study with a similar design. The authors included a case group of 163 women with childbirths after MUS (64 vaginal deliveries, 95 cesarean sections, and four women with both delivery modes) and a control group of 374 women with no deliveries after MUS [157]. The median interval from primary MUS to follow-up was nine years, similar to our study. The primary outcome was subjective SUI (defined as an answer of moderate to great bother on the question “Do you experience urine leakage related to physical activity, coughing or sneezing?”) using the Urogenital Distress Inventory [173]. The rate of subjective SUI was 22 % in the case group and 17 % in the control group (OR 1.4, 95 % CI 0.9 -2.2, $p = 0.46$), which were comparable to the findings of our study (18 % vs. 25 %). However, in contrast to our study, they did not have follow-up data on continence status from both before and after the subsequent pregnancies and deliveries.

One year after publishing Paper I, Tulokas et al. published a similar study from Finland, using the same case-control cohort design [158]. They identified 94 women with subsequent pregnancies after MUS and included a control group of 330 women with no deliveries after MUS, matched by age, operation type, and year of surgery. The median follow-up time in their study was 11 years, and the primary outcome was defined as re-visits for

bothersome stress- or mixed incontinence. They found that re-visits were equally common for women with subsequent pregnancies after MUS compared to the control group (25 % vs. 26 %, OR 0.9, 95 % CI 0.5 – 1.6). However, one-third of the women in the case group experienced recurrence of SUI symptoms before the subsequent pregnancy after MUS. There was no significant difference in the number of repeat operations between the case and control groups (3.2 % vs. 5.2 %, OR 0.6, 95 % CI 0.5 – 1.6, $p = 0.6$) which is in line with the observations presented in Paper I.

Supporting structures in the pelvis that maintain continence might be injured during vaginal delivery [115, 118, 120, 131, 138]. Therefore, concerns have been raised whether vaginal delivery could increase the risk of SUI recurrence in a patient who has previously been treated with MUS [90]. Consequently, many gynecologists would recommend a cesarean section [93]. In our study, the mode of delivery was not associated with the risk of MUS failure or complications during pregnancy and delivery, indicating that vaginal delivery does not affect the MUS efficacy. This is also in line with the other two Nordic studies mentioned above [157, 158]. In our study, the total cesarean section rate was 46 % after MUS. We found a higher proportion of cesarean sections during the first years after MUS was introduced as a surgical method in Norway. Although we were unable to assess the indications for cesarean section, we assume it was the preferred mode of delivery as gynecologists lacked knowledge about what it would mean for the continence status of these women to deliver vaginally. In recent years, however, there has been a trend towards not opposing vaginal delivery after MUS.

Potential risk factors for SUI recurrence were evaluated using logistic regression, adjusting for baseline differences (age and parity) between the case- and control groups. In the multivariate analysis, parity but not age was an independent risk factor for SUI recurrence. In contrast to the Swedish

study, we found that having two or more children before MUS surgery reduced the risk of SUI recurrence. However, after removing the nulliparous women from the analysis, this association was lost. A similar association for nulliparous women was also seen in Paper III when assessing the impact of obstetrical factors on objective failure after MUS, suggesting different pathophysiology for SUI development in nulliparous women. One possibility is that women who develop SUI prior to the pelvic floor challenge of a pregnancy have a stronger genetic disadvantage with poorer connective tissue support than women developing SUI following two pregnancy and delivery events.

High BMI (≥ 30) at the time of MUS surgery was a strong risk factor for recurrent or persistent SUI symptoms, independently of childbirth after MUS. We found a similar correlation between obesity and both subjective and objective short-term MUS failure also in Paper III. This confirms obesity as a strong independent risk factor for SUI, in line with the findings from others showing that obese women have approximately two times the risk of SUI as non-obese women [7, 50, 51]. Several published studies have also demonstrated poorer outcomes after MUS in women with high BMI [174, 175].

5.2.2 The reliability and completeness of NFIR

The validation study of the Norwegian Female Incontinence Registry (NFIR), presented in Paper II, revealed high accuracy for the key variables selected for validation. Furthermore, the completeness of the Registry has improved and now covers almost all urinary incontinence surgeries performed in Norway. Two other Scandinavian countries have similar registries for their prolapse and incontinence surgeries.

The Danish Urogynecological Database (DugaBase) was established in 2006. It collects information on both POP and SUI procedures with almost complete national coverage. In 2012, Guldberg and co-workers published the results from a validation study of Dugabase, similar to the study in Paper II. They found high to excellent inter-rater reliability for most of the variables selected for validation, indicating high accuracy of the data registered in the database [176].

The Swedish National Quality Register of Gynecological Surgery (GynOP) was established in 1997 [68]. It includes all major gynecological procedures performed at both public and private hospitals in Sweden, with follow-up two and eight months after surgery. Incontinence surgery procedures have been registered in this Registry from 2006 and onwards with almost complete national coverage. The Registry has not formally been validated. However, the Registry application includes several validation functions enhancing data accuracy.

Health registers are an attractive source for medical research since they are easily accessible, contain large amounts of data that would otherwise be unavailable, pose little risk of bias, and provide low-cost data access [177]. However, the value of a health registry is strongly determined by the quality of the contained data [177]. Assessment of data quality helps in identifying the data's strengths and limitations. Quality, as defined by the International Organization for Standardization (ISO), is "the totality of features and characteristics of an entity that bears on its ability to satisfy stated and implied needs" [178]. In the context of a health registry, data quality has been defined as "the totality of features and characteristics of a dataset, that bears on its ability to satisfy the needs that result from the intended use of the data" [179].

Numerous data quality attributes have been suggested, but they overlap or have different interpretations, sometimes based on vague definitions [177, 179–181]. An evidence-based or best practice method to evaluate data quality is currently lacking. However, two frequently cited data quality attributes are data accuracy and completeness [179]. In 2009, Bray and Perkin proposed a framework for evaluating data quality in cancer registries [182, 183]. Although primarily developed for cancer registries, the framework has proved useful in assessing data quality in other Norwegian health registries [184–186]. The framework consists of four quality dimensions:

1. Comparability – The extent to which data is comparable across time and geographic areas
2. Accuracy/validity – The proportions of cases within a registry with a given characteristic that genuinely have that attribute
3. Completeness – The extent to which all cases in the target population are included in the registry
4. Timeliness – Time from event took place to inclusion in the register

Accuracy and completeness were chosen for assessment in Paper II, as they were considered the most important factors for valid research results.

According to Bray and Perkin, the preferred method for assessing data accuracy is to establish a gold standard by conducting an independent re-abstraction and recoding of the source data, followed by a comparison between the registry and the gold standard [182]. However, some variables may lack objective true source data, making such validation challenging. Another method, as used in Paper II, is by comparing key variables selected for validation with the patients' medical records as a reference, assuming

that the source data (patients' medical records) represent "true values." Inter-rater agreement and intraclass correlations were chosen to obtain information on accuracy in the absence of a "true value."

As opposed to validity, reliability relates to data reproducibility or stability, not whether the data reflects the "true values." In Bray and Perkin's framework, reliability is an integrated part of accuracy/validity. The target metaphor (**Figure 6**) is often used to illustrate the relationship between reliability and validity [187]. The center of the target (the bull's eye) is what the researcher is trying to measure. In the first target of **Figure 6**, the high reliability does not imply valid measures. An instrument may be incorrectly calibrated, resulting in consistent but incorrect measurements. In the second target, unreliable measures can obtain valid results on a group level if the measures are evenly spread around the true value. In the third target, the measures are neither reliable nor valid. The last target represents valid measures that are also reliable on an individual level.

Figure 6: Reliability vs. validity

Source: Adapted from de Souza [187]

According to Bray and Perkin, completeness is defined as the extent to which all cases in the target population are included in the registry [183].

Information on completeness is important for any health registry, especially for registries reporting incidence rates and survival proportions. The completeness of NFIR has improved over time and now covers almost all

urinary incontinence surgeries performed in Norway and are in line with similar registries in Sweden and Denmark [68, 176]. In contrast to Dugabase in Denmark, reporting to NFIR is not mandatory by law. As Norway provides a public healthcare system for all inhabitants free of charge, most women requiring incontinence surgery will have the procedure performed at a public hospital. Currently, only one private hospital reports to NFIR. Other private hospitals do not report to the Registry. Hence, women having their surgical treatment at a private hospital would not be detected. However, it has been estimated that less than 1 % of female SUI procedures in Norway are performed at private hospitals, thereby not hampering the conclusions of the present study.

5.2.3 The impact of pregnancy and delivery before MUS surgery

The potential impact of a woman's obstetrical history before MUS surgery on short-term subjective and objective failure rates was investigated in Paper III. Using data from a large nationwide maternity Registry which included women having had SUI surgery in Norway in the period from 1998 to 2016, various obstetrical factors in addition to constitutional factors could be evaluated. Initially, the univariate analyses suggested that several obstetrical factors could affect the surgical result of MUS surgery. However, after adjusting for known constitutional factors, none of the obstetrical variables remained independent risk factors for subjective short-term failure after MUS in the final multivariate model. Although no association was found between the obstetrical factors and the subjective result, to our surprise, the nulliparous women had an increased risk of objective failure after MUS. This risk was independent of other constitutional risk factors. We have no explanation for this fact using the current knowledge of SUI development other than theoretically speculate that it might suggest different

pathophysiology in the SUI mechanism for these patients. However, this remains an open question requiring future research.

The present study also confirmed several known risk factors associated with MUS failure, such as high BMI at time of surgery, high preoperative degree of objective leakage, high preoperative symptom load (both for stress and urgency incontinence symptoms), preoperative low maximum urinary flow rate (< 15 ml/s), type of sling utilized and suffering from surgical complications [83, 146, 174, 175, 188–191].

As elaborated in the Introduction section, there is a strong causal relationship between childbearing and the later development of SUI [1, 3–8]. In the EPINCONT-study, SUI prevalence increased with parity, with a relative risk of 1.9 (95 % CI, 1.6–2.2) for primiparous women and 2.3 (95 % CI, 2.0–2.6) for women with two deliveries [3]. The pelvic floor undergoes anatomical, morphological, functional, and hormonal changes during pregnancy and delivery [17, 100, 106, 107]. The underlying pathophysiological mechanism for childbearing and the development of SUI is not fully understood. However, data suggest that reversible or permanent injuries to pelvic floor structures might occur through mechanical forces, inducing increased bladder neck hypermobility and reduced pelvic floor contractility [106, 118, 119, 131].

Several studies have found a higher prevalence of SUI after vaginal delivery than after cesarean section [5, 6, 8, 36–40]. In an extensive systematic review, the risk of developing SUI after vaginal delivery was nearly twice as high as after cesarean delivery [41]. However, studies have also shown that the protective effect of cesarean delivery on SUI diminishes over time and disappears after multiple deliveries [8, 37, 40]. Even though we have extensive knowledge on the impact of pregnancy and delivery for the

development of stress urinary incontinence, it is largely unknown whether the same obstetrical factors (e.g., parity, delivery mode, and fetal factors) also could affect the surgical outcome from SUI surgery. To our knowledge, parity seems to be the only factor studied in the literature [190–192]. Laterza et al. investigated the impact of parity at the time of surgery on short- and long-term outcomes in women undergoing MUS surgery [191]. The authors did a secondary data analysis using data from a previously published randomized study, including 554 women. The study group found that parity had no significant impact on the surgical outcomes after MUS. In a similar randomized study from the US by Richter and co-workers, including 565 women, parity was again not found to impact the objective treatment failure one year after MUS surgery [190]. Furthermore, it has also been shown in a prospective cohort study of 238 women undergoing retropubic MUS operations that the number of vaginal deliveries did not impact short-term sling failure [192]. Even though we knew that others had not found any clear association, our unique possibility of merging large databases with a huge amount of data on pregnancy, delivery, and later SUI surgery compelled us to do a more extensive “deep-dive” into this important research question. By merging two national high-coverage databases, we could obtain larger datasets than what was possible for these other researchers and obtain more complete obstetrical data with negligible recall bias. However, reassuringly, even with our large dataset, neither parity nor any other of the studied obstetrical factors proved to impact the surgical outcome.

Interestingly, instead of finding any clear association between obstetrical factors and the surgical result, being nulliparous was found to be an independent risk factor for objective failure after MUS, even after adjusting for constitutional risk factors. Although pregnancy, and especially vaginal delivery, are known risk factors for SUI, observational studies have reported

that SUI still occurs in 5 % to 11 % of nulliparous women aged 24 to 64 years [3, 7]. As previously elaborated on, this may theoretically be explained by a different underlying mechanism for incontinence in these women and not urethral hypermobility induced by trauma to the pelvic floor.

We initially thought that the observed differences in BMI between nulliparous and parous women in the present study could be the explanatory factor, as overweight and obesity were seen as independent risk factors for MUS failure, which are also in line with other studies [174, 175]. However, having adjusted for BMI in the multivariate model, being nulliparous still remained an independent risk factor for objective failure. Several studies have demonstrated an association between connective tissue quality and pelvic floor dysfunction [56, 57]. A study by Keane et al., examining the collagen status in nulliparous women with genuine SUI, showed significantly less periurethral collagen compared to continent controls, suggesting a possible genetic tissue susceptibility to SUI development [57]. Additional potential explanations for SUI development in nulliparous women might be a dysfunctional pelvic floor due to age-related atrophy of muscles, undiagnosed neurological diseases, or poor urethral sphincter function. Although not significant, a higher prevalence of intrinsic sphincter deficiency (ISD, defined as MUCP $\leq$ 20 cmH₂O) was observed at baseline for the nulliparous women in our study compared to parous women (3.1 % vs. 1.8 %, $p=0.151$). Women with ISD have been shown to have more severe incontinence than women with normal urethral closure function, and studies also demonstrate poorer outcomes after MUS for these women, especially with obturator tapes [83, 167].

Other non-obstetrical factors, previously described in the literature, were also confirmed as risk factors for short-term MUS failure in the present study. Overweight and obesity are strong known risk factors for SUI and MUI [7, 50,

51]. Several studies have evaluated the outcome after MUS operations in obese women with contradictory results [193, 194]. However, a large population-based study published in 2018, including 11,860 women, found a significant dose-dependent relationship between BMI and poor outcomes after retropubic MUS [175]. Barco-Castillo and co-workers found a similar association in a meta-analysis including four randomized controlled trials, with an estimated relative risk (RR) of objective failure 1.62 (95 % CI 1.26 – 2.07) and RR of subjective failure 1.69 (95 % CI 1.32 – 2.16) after retropubic MUS [174].

In the present study, women operated with trans-obturator or mini-slings had a higher risk of failure than women operated with retropubic slings. Several studies have demonstrated higher cure rates after retropubic slings compared to other types, but at the cost of higher risk of surgical complications. In a large meta-analysis that included 15,855 women, patients treated with retropubic slings had higher subjective (OR 0.83, $p = 0.03$) and objective (OR 0.82, $p = 0.01$) cure rates than those receiving trans-obturator slings [189].

A strong association between high preoperative urgency symptom load and failure after MUS was observed in Paper III. Similar associations between preoperative urinary urgency and surgical outcomes after MUS have also been demonstrated by others [146, 195, 196]. However, in two other studies specifically investigating women with stress-dominant mixed urinary incontinence, the presence of urgency symptoms before surgery did not seem to negatively impact the outcome after MUS [150, 197]. One possible explanation for these conflicting results could be that different definitions of cure are used. Nonetheless, patients with MUI should be counseled about the risk of lower cure rates after MUS, and other non-surgical treatments should be considered before surgery.

Several studies have also found that increasing age is a risk factor for poorer outcomes after MUS [145, 146, 198]. In the present study, we could not verify age at the time of surgery as a risk factor for neither subjective nor objective failure. A possible reason could be that women > 67 years (born before 1949) were excluded from the study as these could theoretically have given birth to non-registered children before the inception of the MBRN. However, in a study based on data from approximately the same cohort of women as in Paper III, Engen and co-workers demonstrated a significantly higher risk of poor outcomes for women in their seventh decade or older [145].

6 CONCLUSIONS

The conclusions that can be drawn from this thesis are as follows:

By using data from the NFIR registry, this thesis has shown that women giving birth after mid-urethral sling (MUS) surgery had similar long-term satisfactory outcomes than women without subsequent pregnancies after MUS, with the exception of women undergoing more than one subsequent delivery.

Furthermore, the mode of delivery after MUS did not seem to impact the risk of recurrence of stress urinary incontinence (SUI) symptoms. However, given the small number of patients, the interpretation of delivery mode and multiple post-MUS pregnancies must be interpreted cautiously. The incidence of MUS-related complications during pregnancy and delivery was low, and no severe complications were reported.

This thesis also demonstrates that the Norwegian Female Incontinence Registry (NFIR) contains highly accurate data. There is no evidence that the accuracy has changed over time or that there are differences in accuracy based on the reporting hospitals' surgical volume. The Registry's completeness has improved over time and now contains data on near all women undergoing female incontinence surgery in Norway. Given these observations, we conclude that the NFIR is a reliable tool for research and improving the quality of incontinence surgeries in Norway.

One of the research questions for this thesis was whether pregnancy and delivery before MUS surgery could potentially impact the surgical results. However, the thesis concludes that even though obstetrical factors probably play a significant role in the SUI development, they do not seem to play any significant role in determining the short-term outcomes after MUS surgeries. Surprisingly, this thesis finds that being nulliparous before MUS operations is

an independent risk factor for objective short-term failure, indicating a possible different underlying SUI pathogenesis in these women. As others have shown, we found that constitutional factors such as high body mass index (BMI) at time of surgery, non-retropubic slings, high preoperative urgency- or stress urinary incontinence symptom load, and surgical complications were all factors highly associated with subjective or objective failure after MUS.

7 CLINICAL IMPLICATIONS AND FUTURE STUDIES

Hopefully, this thesis contributes to increased knowledge for both urogynecologists and obstetricians of the reassuring lack of impact from childbirths before and even after mid-urethral sling operations on the surgical outcomes. Understanding the factors associated with treatment failure and success can help clinicians more effectively counsel the patient about realistic expectations and develop potential preventive strategies for SUI relapse.

Based on this thesis's findings, mid-urethral slings (MUS) may be offered to women who have not completed childbearing if the indication for surgery is strong and conservative options have failed. There is no established best practice on the preferred mode of delivery for women who have previously been treated with MUS. However, based on the results from this thesis, vaginal delivery can probably be recommended as the preferred mode of delivery if the woman has previously had uncomplicated vaginal births. As the study included a small sample of women, further data is needed for conclusive recommendations.

The Norwegian Female Incontinence Registry contains high-quality data on a large population of women treated for stress urinary incontinence (SUI). This thesis demonstrates how a health registry represents an invaluable tool when investigating research questions that, for ethical reasons, cannot or should not be performed in prospective observational studies (randomized or non-randomized). It is important to document the strength and limitations of the data contained in a registry to determine its usefulness. Validation studies increase the credibility of registry-based research, as well as identifying potential areas for improvements. However, validation studies have only temporal validity, and efforts to improve data quality should be continuous

and prioritized for all health registries. Hopefully, this thesis might encourage other quality registries to conduct similar validation studies.

This thesis provides evidence that obstetrical factors related to SUI development do not negatively impact the outcomes after MUS. However, the association between being nulliparous and poorer objective outcomes after MUS warrant further research. If being nulliparous truly is an independent risk factor for SUI, this highlights the need for more extensive research into the pathophysiology and treatment options for these women that may very well be different from the women developing SUI as a consequence of having given birth. Whether intensified pelvic floor muscle training (PMT) or other conservative procedures (including weight loss in overweight and obese women) would help to reduce the risk for SUI relapse after MUS in these women is unknown. However, given the general health effects of obtaining normal weight and the lack of adverse side effects of PMT, it is reasonable to offer these pelvic floor supporting options also following surgery to any nulliparous women in need of MUS, as well as to any other women with risk factors for relapse (e.g., obesity).

8 APPENDICES

Appendix 1: Norwegian Female Incontinence Registry Questionnaire

Norwegian female incontinence questionnaire for urinary incontinence																																															
	Pre and postoperative recording <div style="display: flex; justify-content: space-between;"> <div style="text-align: center;"> Date for questionnaire completion <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="margin: 0 5px;">.</div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="margin: 0 5px;">.</div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> </div> </div> <div style="text-align: center;"> patient number <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> </div> </div> </div>																																														
<p>Please answer all questions. (Mark yes, no or not relevant for each alternative in question 1)</p> <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 70%;"></th> <th style="width: 10%; text-align: center;">yes</th> <th style="width: 10%; text-align: center;">no</th> <th style="width: 10%; text-align: center;">not relevant</th> </tr> </thead> <tbody> <tr> <td>1. Do you leak urine?</td> <td></td> <td></td> <td></td> </tr> <tr> <td>when you cough</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> </tr> <tr> <td>when you sneeze</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> </tr> <tr> <td>when you laugh</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> </tr> <tr> <td>when you walk up or down in stairs</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> </tr> <tr> <td>when you raise from bed</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> </tr> <tr> <td>when you lift heavy objects</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> </tr> <tr> <td>during physical activity (running to catch the bus)</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> </tr> <tr> <td>during sports</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> </tr> <tr> <td>during intercourse</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> <td style="text-align: center;">☐</td> </tr> </tbody> </table> <p><i>(Mark only one alternative for each question from 2 - 6))</i></p> <p>2. How often do you leak urine in relation to physical activity, when you laugh, cough or sneeze?</p> <p>☐ never</p> <p>☐ 1 -4 times each month</p> <p>☐ 1 -6 times each week</p> <p>☐ once per day</p> <p>☐ more than once per day</p> <p>3. How large is the amount of urine you usually leak during physical activity or when you laugh, cough or sneeze?</p> <p>☐ nothing</p> <p>☐ drops / moist underwear</p> <p>☐ dripping / wet underwear</p> <p>☐ running / passes through all your clothes</p> <p>☐ running down your legs or down at the floor</p> <p>4. How often do you experience sudden and imperious need to void and urinary leakage before you reach the toilet?</p> <p>☐ never</p> <p>☐ 1 -4 times each month</p> <p>☐ 1 -6 times each week</p> <p>☐ once per day</p> <p>☐ more than once per day</p> <p>5. How large is the amount of urine you usually leak when you experience sudden and imperious need to void and</p> <p>☐ nothing</p> <p>☐ drops / moist underwear</p> <p>☐ dripping / wet underwear</p> <p>☐ running / passes through all your clothes</p> <p>☐ running down your legs or down at the floor</p> <p>6. If you experience symptoms both as those described in question 2 and question 4, what is troubling you the most?</p> <p>☐ leakage during physical activities more than leakage related to urge?</p> <p>☐ leakage during urgency more than during physical activity?</p> <p>☐ equally trouble by leakage during urgency as by leakage during physical activity?</p> <p>☐ I don't have leakage as described in question 2 nor question 4</p> <p><i>(Mark only one alternative for each question 7 - 11)</i></p> <p>7. How many incontinence pads do you use?</p> <p>☐ none ☐ 1 - 3 per week ☐ 4 - 6 per week ☐ 1 - 4 per day ☐ more than 4 per day</p> <p>8. How many times have you been treated for cystitis the last 6 months?</p> <p>☐ none ☐ once ☐ 2 - 3 times ☐ 4 times ☐ more than 4 times</p>					yes	no	not relevant	1. Do you leak urine?				when you cough	☐	☐	☐	when you sneeze	☐	☐	☐	when you laugh	☐	☐	☐	when you walk up or down in stairs	☐	☐	☐	when you raise from bed	☐	☐	☐	when you lift heavy objects	☐	☐	☐	during physical activity (running to catch the bus)	☐	☐	☐	during sports	☐	☐	☐	during intercourse	☐	☐	☐
	yes	no	not relevant																																												
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during sports	☐	☐	☐																																												
during intercourse	☐	☐	☐																																												

Norwegian female incontinence questionnaire for urinary incontinence

9. How often do you avoid activities (for example a hobby, physical training or going out) because you are afraid of leaking urine)?

☐ never ☐ seldom ☐ sometimes ☐ often ☐ always

10. How often do you avoid places and situations where you are aware of that a toilet is not easily available?

☐ never ☐ seldom ☐ sometimes ☐ often ☐ always

11. Is your sexual life influenced by your leakage problem? (To be answered before treatment)

☐ not relevant
☐ substantially improved
 ☐ some improvement
 ☐ unchanged
 ☐ some deterioration
 ☐ substantial deterioration

(Mark yes, no or not relevant for each question under 12)

12. Does your urinary leakage influence? yes no not relevant

your vacation?	☐	☐	☐
your family life?	☐	☐	☐
your social life (going out, meeting friends?)	☐	☐	☐
your sleep?	☐	☐	☐

(Mark only one alternative for each question 13 - 14)

13. Is your sexual life influenced by your leakage problem? (To be answered after treatment)

☐ not relevant
 ☒ substantially improved
 ☐ some improvement
 ☐ unchanged
 ☐ some deterioration
 ☐ substantial deterioration

14. Are you satisfied with the result of the treatment you have received to cure your urinary leakage?

☐ very satisfied ☐ moderately satisfied ☐ neither satisfied nor unsatisfied ☐ moderately unsatisfied ☐ very unsatisfied

Please do not fill in. Will be filled in by a physician

<input type="text"/>	<input type="text"/>	investigator ID number	maximum closure pressure cm H ₂ O	<input type="text"/>	<input type="text"/>	complication ☐ yes ☐ no
date of incontinence surgery		<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	bladder perforation ☐ yes ☐ no
<input type="text"/>	<input type="text"/>	<input type="text"/>	leakage during stress test gr.	<input type="text"/>	<input type="text"/>	hematoma > 3 cm ☐ yes ☐ no
<input type="text"/>	<input type="text"/>	<input type="text"/>	residual urine ml.	<input type="text"/>	<input type="text"/>	superficial wound infection ☐ yes ☐ no
<input type="text"/>	<input type="text"/>	surgeon ID number	maximum flow ml/sec.	<input type="text"/>	<input type="text"/>	deep wound infection ☐ yes ☐ no
<input type="text"/>	<input type="text"/>	surgical procedure number	height in cm.	<input type="text"/>	<input type="text"/>	catheter > 1 week ☐ yes ☐ no
<input type="text"/>	<input type="text"/>	number of earlier surgical procedures to cure incontinence	weight in kilo	<input type="text"/>	<input type="text"/>	catheter > 1 month ☐ yes ☐ no
☐ yes ☐ no	incontinence surgery combined with vaginal surgery		date of stopped and not completed incontinence surgery	<input type="text"/>	<input type="text"/>	tape adjusted surgically ☐ yes ☐ no
☐ yes ☐ no	incontinence surgery performed previously in our department		date of tape surgically adjusted	<input type="text"/>	<input type="text"/>	gut perforation ☐ yes ☐ no
<input type="text"/>	<input type="text"/>	number of micturitions 24 hours	date of tape transected	<input type="text"/>	<input type="text"/>	vascular lesion ☐ yes ☐ no
<input type="text"/>	<input type="text"/>	<input type="text"/>	date of surgery for mesh exposure	<input type="text"/>	<input type="text"/>	bleeding > 500 ml. ☐ yes ☐ no
<input type="text"/>	<input type="text"/>	mean voiding volume ml.	date of complete removal of tape	<input type="text"/>	<input type="text"/>	urethral lesion ☐ yes ☐ no
<input type="text"/>	<input type="text"/>	leakage during 24 hours pad test gr.				urinary tract infection ☐ yes ☐ no
other complications						<14 days after surgery
						pain 0 to 10 <input type="text"/>
						<div style="border: 1px solid black; padding: 5px;"> ☐ none ☐ less than 2 weeks ☐ 2 to 12 weeks ☐ more than 12 weeks </div>

Appendix 2: Questionnaire – Paper I – Cases

Spørreskjema for urinlekkasje – Cases

Navn og personnummer
(Barcode-lapp)

Dato for innfylling av skjemaet

NKIR-nr.

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Generell informasjon

1. Vekt i kg: _____ Høyde i cm: _____ Alder i år: _____

2. Røyk: _____ sig/dag (snitt av siste uke)

Kryss av ja, nei eller ikke aktuelt for alle alternativer i spørsmål 3

3. Lekker du urin?

Når du hoster	☐ Ja	☐ Nei	
Når du nyser	☐ Ja	☐ Nei	
Når du ler	☐ Ja	☐ Nei	
Når du går i trapper	☐ Ja	☐ Nei	
Når du står opp av sengen	☐ Ja	☐ Nei	
Når du løfter tungt (tunge bæreposer)	☐ Ja	☐ Nei	☐ Ikke aktuelt
Ved fysisk aktivitet (løpe for å nå bussen)	☐ Ja	☐ Nei	☐ Ikke aktuelt
Ved sportsaktiviteter	☐ Ja	☐ Nei	☐ Ikke aktuelt
Ved samleie	☐ Ja	☐ Nei	☐ Ikke aktuelt

4. Hvor ofte lekker du urin i forbindelse med fysisk aktivitet, når du ler, hoster eller nyser?

- ☐ Aldri
☐ 1 – 4 ganger pr måned
☐ 1 – 6 ganger pr uke
☐ 1 gang pr dag
☐ Mer enn 1 gang pr dag

5. Hvor stor mengde urin lekker du vanligvis ved fysisk aktivitet, når du ler, hoster eller nyser?

- ☐ Ingen
☐ Dråper/fuktig undertøy
☐ Drypper/vått undertøy
☐ Renner/går gjennom ytterklær
☐ Renner nedover bena eller ned på gulvet

6. Hvor ofte opplever du plutselig sterk trang til å late vannet og lekker urin før du når frem til toalettet?

- ☐ Aldri
☐ 1 – 4 ganger pr måned
☐ 1 – 6 ganger pr uke
☐ 1 gang pr dag
☐ Mer enn 1 gang pr dag

7. Hvor stor mengde urin lekker du vanligvis når du har trang til å late vannet og lekker urin før du når frem til toalettet?

- ☐ Ingen
☐ Dråper/fuktig undertøy
☐ Drypper/vått undertøy
☐ Renner/går gjennom ytterklær
☐ Renner nedover bena eller ned på gulvet

8. Dersom du har symptomer både som i spørsmål 4 og spørsmål 6, hva er du mest plaget av?

- ☐ Lekkasje ved fysisk aktivitet mer enn lekkasje ved trang
☐ Lekkasje ved trang mer enn ved lekkasje ved fysisk aktivitet
☐ Like mye plaget av lekkasje ved trang som ved lekkasje ved fysisk aktivitet
☐ Har ikke lekkasje hverken som under spørsmål 7 eller spørsmål 9

KRYSS AV ETT ALTERNATIV FOR HVERT AV SPØRSMÅLENE 9 – 14

9. **Hvor mange inkontinensbind bruker du?**
☐ Ingen ☐ 1-3 pr uke ☐ 4 – 6 pr uke ☐ 1- 4 pr dag ☐ Mer enn 4 pr. dag
10. **Hvor mange ganger har du fått behandling for blærekatarr de siste 6 månedene?**
☐ Aldri ☐ 1 gang ☐ 2 – 3 ganger ☐ 4 ganger ☐ Mer enn 4 ganger
11. **Hvor ofte unnlater du aktiviteter (f.eks. en hobby, fysisk trening eller gå ut) fordi du er redd for å lekke?**
☐ Aldri ☐ Sjelden ☐ Av og til ☐ Ofte ☐ Alltid
12. **Unngår du steder og situasjoner hvor du vet at toalett ikke er lett tilgjengelig?**
☐ Aldri ☐ Sjelden ☐ Av og til ☐ Ofte ☐ Alltid
13. **Påvirker din urinlekkasje**
Dine ferier? ☐ Ja ☐ Nei ☐ Ikke aktuelt
Ditt familieliv ☐ Ja ☐ Nei ☐ Ikke aktuelt
Ditt sosiale live (å gå ut, treffe venner)? ☐ Ja ☐ Nei ☐ Ikke aktuelt
Din nattesøvn ☐ Ja ☐ Nei ☐ Ikke aktuelt
14. **Er du fornøyd med det nåværende resultatet av din behandling for hostelekkasje?**
☐ Veldig fornøyd ☐ Litt fornøyd ☐ Verken fornøyd eller misfornøyd
☐ Litt misfornøyd ☐ Veldig misfornøyd
15. **Har du etter inkontinensoperasjonen operert bort livmoren?** ☐ Nei ☐ Ja
16. **Har du etter lekkasjeoperasjonen blitt operert for underlivsfremfall?** ☐ Nei ☐ Ja
17. **Har du hatt følelsen av at det er vanskelig å tømme blæren etter operasjonen?**
☐ Nei ☐ Ja, detaljer: _____
18. **Bruker du nå behandling med inkontinensmedisin?**
(Betmiga, Detrusitol, Vesicare, Emselex, Toviaz eller Kentera)?
☐ Nei ☐ Ja
19. **Har du etter fødselen gjennomgått ny lekkasjeoperasjon?** ☐ Nei ☐ Ja
Metode: _____ (fylles ut av studielege/sykepleier) Evt. år opr: _____
20. **Har du senere mottatt annen behandling mot urinlekkasje** ☐ Nei ☐ Ja
☐ Bekkenbunnstrening ☐ Medikamentell behandling ☐ Botox ☐ Nevrostimulator
☐ Annet: _____

Spørreskjema for urinlekkasje – PregnanT-studien

Navn og personnummer
(Barcode-lapp)

Dato for innfylling av skjemaet

Pasientnr. (NUGG-nr)

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21. Antall fødsler *før* inkontinensoperasjon: _____ vaginal forløsning(er) _____ keisersnitt
22. Antall fødsler *etter* inkontinensoperasjon: _____ vaginal forløsning(er) _____ keisersnitt
Dersom keisersnitt i spørsmål 22, var det ☐ planlagt ☐ akutt?
23. Ammet du barnet/barna du fødte etter inkontinensoperasjonen?
☐ Nei ☐ Ja, i _____ måneder
24. Hvordan vil du beskrive din lekkasjesituasjon nå sammenlignet med før lekkasjeoperasjon?
☐ Kureret ☐ Bedre ☐ Uendret ☐ Verre
25. Hvordan vil du beskrive din lekkasjesituasjon før du ble gravid (etter lekkasjeoperasjonen)?
☐ Kureret ☐ Bedre ☐ Uendret ☐ Verre
26. Dersom lekkasjesituasjonen (ved hoste, latter, fysisk aktivitet) ble verre, når merket du det?
☐ Ikke aktuelt ☐ Under svangerskapet ☐ Etter fødsel
27. Dersom lekkasjesituasjonen (ved hoste, latter, fysisk aktivitet) ble verre under/etter svangerskapet, hvordan vil du beskrive lekkasjesituasjonen i tiden etter fødsel fram til i dag?
☐ Ikke aktuelt ☐ Uendret (like ille) ☐ Forbigående (blitt bedre) ☐ Forbigående (blitt verre)
28. Har det vært det komplikasjoner knyttet til lekkasjeoperasjonen under svangerskapet eller etter fødsel?
☐ Nei ☐ Ja
Hvis ja, hva slags komplikasjon (eks båndet ble synlig i skjeden, tilbakevendende urinveisinfeksjoner, vannlatningsvansker eller annet)?

29. Var det vanskelig å late vannet under svangerskapet?
☐ Nei ☐ Ja
30. Var der vanskelig å late vannet etter fødsel?
☐ Nei ☐ Ja
31. Hadde du behov for å benytte kateter under svangerskapet eller etter fødsel for å tømme blæren?
☐ Nei ☐ Ja

Appendix 3: Questionnaire – Paper I – Controls

Spørreskjema for urinlekkasje – Kontroller

Navn og personnummer (Barcode-lapp)
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Dato for innfylling av skjemaet

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NKIR-nr.

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Generell informasjon

1. Vekt i kg: _____ Høyde i cm: _____ Alder i år: _____
2. Røyk: _____ sig/dag (snitt av siste uke)

Kryss av ja, nei eller ikke aktuelt for alle alternativer i spørsmål 4

3. Lækker du urin?

Når du hoster	☐ Ja	☐ Nei	
Når du nyser	☐ Ja	☐ Nei	
Når du ler	☐ Ja	☐ Nei	
Når du går i trapper	☐ Ja	☐ Nei	
Når du står opp av sengen	☐ Ja	☐ Nei	
Når du løfter tungt (tunge bæreposer)	☐ Ja	☐ Nei	☐ Ikke aktuelt
Ved fysisk aktivitet (løpe for å nå bussen)	☐ Ja	☐ Nei	☐ Ikke aktuelt
Ved sportsaktiviteter	☐ Ja	☐ Nei	☐ Ikke aktuelt
Ved samleie	☐ Ja	☐ Nei	☐ Ikke aktuelt

4. Hvor ofte lekker du urin i forbindelse med fysisk aktivitet, når du ler, hoster eller nyser?

- ☐ Aldri
☐ 1 – 4 ganger pr måned
☐ 1 – 6 ganger pr uke
☐ 1 gang pr dag
☐ Mer enn 1 gang pr dag

5. Hvor stor mengde urin lekker du vanligvis ved fysisk aktivitet, når du ler, hoster eller nyser?

- ☐ Ingen
☐ Dråper/fuktig undertøy
☐ Drypper/vått undertøy
☐ Renner/går gjennom ytterklær
☐ Renner nedover bena eller ned på gulvet

6. Hvor ofte opplever du plutselig sterk trang til å late vannet og lekker urin før du når frem til toalettet

- ☐ Aldri
☐ 1 – 4 ganger pr måned
☐ 1 – 6 ganger pr uke
☐ 1 gang pr dag
☐ Mer enn 1 gang pr dag

7. Hvor stor mengde urin lekker du vanligvis når du har trang til å late vannet og lekker urin før du når frem til toalettet?

- ☐ Ingen
☐ Dråper/fuktig undertøy
☐ Drypper/vått undertøy
☐ Renner/går gjennom ytterklær
☐ Renner nedover bena eller ned på gulvet

8. Dersom du har symptomer både som i spørsmål 4 og spørsmål 6, hva er du mest plaget av?

- ☐ Lekkasje ved fysisk aktivitet mer enn lekkasje ved trang
☐ Lekkasje ved trang mer enn ved lekkasje ved fysisk aktivitet
☐ Like mye plaget av lekkasje ved trang som ved lekkasje ved fysisk aktivitet
☐ Har ikke lekkasje hverken som under spørsmål 7 eller spørsmål 9

9. **Hvor mange inkontinensbind bruker du?**
☐ Ingen ☐ 1-3 pr uke ☐ 4 – 6 pr uke ☐ 1- 4 pr dag ☐ Mer enn 4 pr. dag

10. **Hvor mange ganger har du fått behandling for blærekatarr de siste 6 månedene?**
☐ Aldri ☐ 1 gang ☐ 2 – 3 ganger ☐ 4 ganger ☐ Mer enn 4 ganger

11. **Hvor ofte unnlater du aktiviteter (f.eks. en hobby, fysisk trening eller gå ut) fordi du er redd for å lekke?**
☐ Aldri ☐ Sjelden ☐ Av og til ☐ Ofte ☐ Alltid

12. **Unngår du steder og situasjoner hvor du vet at toalett ikke er lett tilgjengelig?**
☐ Aldri ☐ Sjelden ☐ Av og til ☐ Ofte ☐ Alltid

13. **Påvirker din urinlekkasje**
Dine ferier? ☐ Ja ☐ Nei ☐ Ikke aktuelt
Ditt familieliv ☐ Ja ☐ Nei ☐ Ikke aktuelt
Ditt sosiale live (å gå ut, treffe venner)? ☐ Ja ☐ Nei ☐ Ikke aktuelt
Din nattesøvn ☐ Ja ☐ Nei ☐ Ikke aktuelt

14. **Er du fornøyd med det nåværende resultatet av din behandling for hostelekkasje?**
☐ Veldig fornøyd ☐ Litt fornøyd ☐ Verken fornøyd eller misfornøyd
☐ Litt misfornøyd ☐ Veldig misfornøyd

15. **Har du etter inkontinensoperasjonen operert bort livmoren?** ☐ Nei ☐ Ja

16. **Har du etter lekkasjeoperasjonen blitt operert for underlivsfall?** ☐ Nei ☐ Ja

17. **Har du hatt følelsen av at det er vanskelig å tømme blæren etter operasjonen?**
☐ Nei ☐ Ja, detaljer: _____

18. **Bruker du nå behandling med inkontinensmedisin? (Betmiga, Detrusitol, Vesicare, Emselex, Toviaz eller Kentera)?**
☐ Nei ☐ Ja

19. **Har du gjennomgått ny operasjon mot urinlekkasje ?** ☐ Nei ☐ Ja
Metode: _____ (fylles ut av studielege) Evt. år opr: _____

20. **Har du senere mottatt annen behandling mot urinlekkasje** ☐ Nei ☐ Ja
☐ Bekkenbunnstrening ☐ Medikamentell behandling ☐ Botox ☐ Nevrostimulator
☐ Annet: _____

21. **Antall fødsler før inkontinensoperasjon:** ____ vaginal fødsel(er) ____ keisersnitt

22. **Ble du forløst med vakum eller tang?** ☐ Nei ☐ Ja ☐ Ikke aktuelt

23. **Hvor mye veide barnet(a)**

24. **Tilkom det under fødsel rift av lakkemuskelen til endetarmen (sfinkterskade) ?**
☐ Nei ☐ Ja
Type: _____ (fylles ut av studielege)

25. **Har du etter fødsel hatt plager med å holde på luft og/eller avføring?** ☐ Nei ☐ Ja

9 ERRATA

Abbreviations for different types of corrections:

Cor – correction of language

Cpltf – change of page layout or text format

Page	Reference	Original text	Type of correction	Corrected text
103	5	PhD MGM, PhD SÅM, BSc MM, PhD IMM...	Cor	Gyhagen M, Åkervall S, Molin M, Milsom I...
105	21	L G...	Cor	Lose G...
113	105	DIETZ HP, ELDRIDGE A, GRACE M, CLARKE B...	Cpltf	Dietz HP, Eldridge A, Grace M, Clarke B...
113	111	Brummen HJV, Bruinse HW, Pol GVD, et al...	Cpltf	Brummen HJV, Bruinse HW, Pol GVD, et al...
116	135	...INJURY TO INNERVATION OF PELVIC FLOOR SPHINCTER MUSCULATURE IN CHILDBIRTH...	Cpltf	...Injury to innervation of pelvic floor sphincter musculature in childbirth...
116	138	ALLEN RE, HOSKER GL, SMITH ARB, WARREL DW...	Cpltf	Allen RE, Hosker GL, Smith ARB, Warrel DW...

Paper II:

Result section:

The overall agreement concerning the surgery should be 96.8 % (not 97.5 %)

Table 2:

Type of SUI surgery performed:

The observed agreement should be 96.8 % (not 97.5 %)

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<https://doi.org/10.1007/s00192-016-2995-7>

PAPER II

The completeness and accuracy of the Norwegian Female Incontinence Registry

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Funding information

The study was funded by both Oslo University Hospital and The Norwegian Female Incontinence Registry and also supported by a grant from the Norwegian Medical Association (no. 14/1695).

Abstract

Introduction: Medical quality registries have gained popularity as tools for monitoring the quality of medical treatments and they serve as data sources for research. The Norwegian Female Incontinence Registry (NFIR) was established in 1998 to monitor and improve the quality of surgery for women with stress and mixed urinary incontinence in Norway and to collect data for research. This study aimed to assess the completeness and accuracy of the Norwegian Female Incontinence Registry, and potential differences in data accuracy over time and according to surgical volume of the reporting hospitals.

Material and methods: A random selection of 300 women from a total of 20 610 operated for urinary incontinence between 1998 and 2016 reported to the Norwegian Female Incontinence Registry from 28 public hospitals were selected for validation. The database completeness was estimated for 2008–2017 by comparing surgical procedures registered both in the Norwegian Female Incontinence Registry and the Norwegian National Patient Registry. Historical data recorded in the Registry for 10 selected key variables were extracted and compared with the patients' individual medical records at the reporting hospitals as reference. The reviewers were blinded to the previously stored information. The intraclass correlation coefficient for continuous variables and Cohen's kappa for categorical variables were calculated.

Results: Primary source data on 285 of the 300 women selected from Norwegian Female Incontinence Registry were successfully retrieved. The completeness of the registry has increased from 61% in 2008 to 99% in 2017. The national coverage has increased from 12 reporting departments in 1998 to all 38 public departments performing female incontinence surgery in 2017. Excellent accuracy was found for both continuous variables (intraclass correlation coefficient >0.94) and categorical variables (Cohen's kappa >0.86). No differences in data accuracy were found comparing

Abbreviations: CI, confidence interval; ICC, intraclass correlation coefficients; NFIR, Norwegian Female Incontinence Registry; NPR, Norwegian Patient Registry; SUI, stress urinary incontinence.

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high-volume hospitals with low-volume hospitals, or when comparing data accuracy over time.

Conclusions: The Norwegian Female Incontinence Registry is a reliable tool for quality assessment of incontinence surgery and research. The registry completeness has improved over time and now contains data on nearly all women undergoing incontinence surgery in Norway.

KEYWORDS

quality of healthcare, registries, reliability, stress urinary incontinence, validation studies

1 | INTRODUCTION

The importance of medical quality registries has been increasingly recognized over the last decades, as high-quality registries are invaluable in monitoring unselected populations and improving the quality of health services and serve as a data source for research. As a result, the number of local and national quality is increasing. Several registries, particularly in the Nordic countries, include personal identifiers that facilitate long-term follow-up within registries and linkage between registries.

Stress urinary incontinence is a common condition affecting approximately 15% of women over the age of 18, and it may have a significant impact on the quality of life for these women.^{1,2} Surgical treatment for stress urinary incontinence is usually recommended when conservative treatment options have failed. It is important to evaluate which surgical method ensures an optimal outcome for the individual woman. The Norwegian Female Incontinence Registry (NFIR) was established with the purpose of monitoring and improving the quality of incontinence surgery for women with stress and mixed urinary incontinence in Norway.³ It is one of the oldest continuously recording medical quality registries within the field of urogynecology that provides annual reports analyzing a wide range of pre-, per- and postoperative variables. The accumulated data in such registries have also proven to be a valuable source for research.^{4,5} However, data used in medical research need to be of high quality in order to draw valid and reliable conclusions.⁶

In the present study, we therefore aimed to evaluate the completeness of the Norwegian Female Incontinence Registry and validate the accuracy of 10 selected key variables in the registry. Furthermore, we wanted to examine whether there have been differences in data accuracy over time and based on the surgical volume of the reporting hospitals.

2 | MATERIAL AND METHODS

This was a validation study of the completeness and accuracy of the NFIR. The registry was established in 1998 for women undergoing surgery for female urinary incontinence, financially supported by the health care authorities.³ The hospital departments report

Key message

The Norwegian Female Incontinence Registry contains at present, data on nearly all women undergoing incontinence surgery in Norway and is a reliable tool for quality assessment of incontinence surgery and research.

their pre- and postoperative subjective patient-reported data and objective clinical and urodynamic data, including type of incontinence procedure and complications to the registry. Subjective data is retrieved by a validated short-form urinary incontinence disease-specific questionnaire in Norwegian.⁷ Subjective and objective data are initially registered on standardized paper questionnaires by specially trained nurses or the surgeon. The completed questionnaires are subsequently entered into the local incontinence registry, usually immediately after the surgery or after discharge. Data are transferred to the NFIR every 6 months. From 2016, all public hospitals performing female incontinence surgery in Norway were instructed by their Regional Health Authority to report their data to the registry, and since 2017, all 38 public hospitals performing these surgeries have reported their data to NFIR. The registry develops annual reports on a range of different clinical variables, the most important being results and complication rates for both reporting department and individual surgeons performing female incontinence surgeries in Norway.

The Norwegian Data Protection Authority approved the establishment of the NFIR in 1998. Written informed consent is obtained from all participating women before the data are exported to the national registry in a de-identified form. The code-list for patient identification is kept at the reporting hospital. Patient data from patients not signing the consent form are exported to the registry as anonymous data (lacking a code-list at the reporting hospital).

The Norwegian Patient Registry (NPR) was established in 1997 as a national administrative health registry for all public hospitals in Norway, including private hospitals with public reimbursements contracts with the public regional health authorities.⁸ The registry contains information on health-related data such as dates of admission

and discharge, the primary and secondary discharge diagnoses according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) and codes for diagnostic and therapeutic procedures on all hospitalizations and outpatient visits according to the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical and Medical Procedures (NCSP and NCMP). Data from the hospital patient administrative systems are extracted and transferred to NPR every 4th month.

The study population of this study consisted of women who had previously undergone incontinence surgery for stress or mixed urinary incontinence between 1998 and 2016 and who had completed a physical follow-up at the hospital 6-12 months after the surgery. Women who were unable to attend or who instead had only returned the validated follow-up questionnaire by mail, were excluded. At the time of data collection for this study, 28 of 38 public hospital departments performing female incontinence surgery in Norway were reporting data to the registry. To exclude any selection bias for the women randomized for validation, a sensitivity analysis was performed comparing age at time of surgery, body mass index and the key variables between both the randomized sample of 285 and the total registry population, and between randomized women with complete datasets and the total registry population.

All study women had consented to have their data stored in the NFIR in a de-identified form, making it possible to use the code-list at the reporting hospitals to retrace the completely registered medical charts data. A total of 300 women were selected for study inclusion and data validation by using a random number generator. A list containing all selected unique local NFIR identification numbers was sent by NFIR to each of the contributing hospital departments reporting to the NFIR for patient identification. The patients' medical records at the reporting hospitals were chosen as the primary data source for data reference for women selected for validation and identified by the unique NFIR number coupled to the code-list. The local surgeon or specially trained nurse was then asked systematically to review the patient's medical records and retrieved information on the following 10 selected key variables:

- Date of surgery
- Preoperative cough-jump stress test (g)⁹
- Preoperative post-void residual urine (mL)
- Preoperative maximum urinary flow rate (mL/s)
- Type of stress urinary incontinence surgery performed
- Complications dichotomized into yes or no (see Appendix S1 for complete list of complications reported to the Registry)
- Postoperative (6-12 months) cough-jump stress test (g)⁹
- Postoperative (6-12 months) post-void residual urine (mL)
- Postoperative (6-12 months) maximum flow rate (mL/s)
- Treatment satisfaction (6-12 months postoperatively)

Treatment satisfaction was in this study defined as the percentage of women answering "very satisfied" with their treatment when given the choices "very satisfied", "moderately satisfied", "neither satisfied nor dissatisfied", "moderately dissatisfied" and "very

dissatisfied". All reviewers were blinded to what was previously reported to and stored in the national (NFIR) registry. The retrieving and reviewing of data from the patients' medical records was performed from June 2018 through August 2019. After data on the 10 selected key variables for each woman were sent back to the NFIR, these data were compared with data previously reported to and stored in the national NFIR.

2.1 | Statistical analyses

The sample size of 300 selected for the validation process was determined based on recommendations from a statistician and sample size calculations for Cohen's kappa.¹⁰ A sample of at least 221 cases was necessary to test for a statistical difference between substantial (0.80) and excellent (0.90) kappa values with a 90% power and 5% significance level.

To exclude any selection bias for the included women in the study group, a sensitivity analysis was performed comparing the age at surgery, body mass index and the key variables for the sample of 285, for those women in the study with complete information on the selected variables and for the entire register.

For categorical variables, the inter-rater agreement is presented as observed agreement and chance-corrected proportional agreement (Cohen's kappa) with 95% confidence intervals. The Quadratic weighted kappa was used when analyzing ordinal variables.

The following qualitative terms were attached to the kappa value suggested by Landis and Koch:¹¹ Slight agreement 0-0.20, fair agreement 0.21-0.40, moderate agreement 0.41-0.60, substantial agreement 0.61-0.80, and excellent agreement >0.80. Cases with missing values were excluded from the analysis.

Intraclass correlation coefficients (ICC) were calculated for continuous variables. ICC is a reliability index in test-retest analysis and is calculated by comparing the variability of measurements of the same subject by multiple observers measuring the same quantity.¹² ICC values range between 0 and 1, with values closer to 1 representing stronger reliability. Since there were different groups of women (from different hospitals) rated by different sets of raters (one at each hospital), a one-way random-effects ANOVA model was chosen for calculating the ICC.¹² The time variable "Date of surgery" was re-calculated as days since surgery at the time of data analysis. To show the magnitude of the disagreement, we calculated the mean of the differences between the raters with 95% confidence interval.

The database completeness was defined as the proportion of women with a urinary incontinence operation code registered both in the NFIR and the Norwegian National Patient Registry (NPR) regardless of the registration being incomplete on some variables. Completeness was estimated for the last decade (2008-2017). Before 2008, the hospitals reported only anonymous data to the NPR and therefore it was not possible to evaluate NFIR completeness before this time. Since 2013, the NFIR has implemented a "two-way" method for evaluating completeness to enhance accuracy further. Urinary incontinence operation codes are now annually

compared both with registered NPR data and directly by linking the database to the hospitals' local administrative system, enabling correction of incorrect reported data from the hospitals to NPR.

A multiple linear regression analysis was run to examine whether there was a difference in accuracy over time and between high and low volume hospital departments. The measured difference between medical records and the registry values for continuous variables was used as dependent variables in the regression model. The independent variable used was high-volume vs low-volume departments. High-volume departments in our study included the five hospitals that perform the highest annual number of incontinence surgeries (>150 annually).

Statistical analyses were performed using Statistical Package for the Social Sciences version 23.0 (IBM SPSS), and STATA: Software for Statistics and Data Science version 16.0 (StataCorp). A significance level of 5% was used.

2.2 | Ethical approval

The study was approved both by the Regional Committee for Medical and Health Research Ethics in Norway (#2015/434, 15 April 2015) and the Institutional Personal Data Officer at Oslo University Hospital. All patients had signed a written consent at the time of data reporting to the NFIR. As this study was considered a data quality assurance study of data already collected, additional written consent was not required.

3 | RESULTS

The Norwegian Female Incontinence registry (NFIR) contained data from 28 873 patients from 38 public departments at the time of data extraction (March 2018), of which 20 610 fulfilled the study inclusion criteria (Figure 1). A random sample of 300 cases across the reporting departments was extracted and included in the study. The randomization included patients from 27 of 28 reporting departments. No women were randomly selected from department no. 28. Twelve patients who originally were selected for validation, had to be excluded due to six non-responding departments. An additional three patients were excluded, as the information needed for validation could not be retrieved at the reporting department. The final study analyses were therefore performed on the remaining 285 included patients (95%) at 21 departments. The 10 key variables selected for validation were reviewed in the patients' individual hospital medical records and compared with the information stored in the national Norwegian Female Incontinence Registry.

The sensitivity analyses, comparing baseline characteristics between the women randomized for validation and the total registry population, showed no significant differences, suggesting minimal unintentional selection bias in the study sample (Table 1).

The NFIR completeness is shown in Figure 2. The completeness increased from 61% in 2008 to 99% in 2017 for the hospitals

FIGURE 1 Flowchart of the study population

reporting to the registry. The national coverage increased from 12 reporting departments in 1998 to all 38 public departments and one private hospital performing female incontinence surgery in 2017.

The inter-rater agreements for the non-continuous variables are presented in Table 2 and the ICC for the continuous variables in Table 3. For the variables concerning type of surgery, complications and treatment satisfaction, we found excellent agreements ($\kappa > 0.86$) (Table 2). The overall agreement concerning the type of surgery was 97.5%. Only nine women (3.2%) had an incorrectly entered type of stress urinary incontinence surgery into the national database. Five of these, who had undergone surgery with the retropubic tension-free vaginal tape (TVT) procedure, had been incorrectly registered as having had a periurethral bulking procedure ($n = 2$) or a tension-free vaginal tape obturator TVT-O procedure ($n = 3$). Furthermore, four patients who had undergone

TABLE 1 Baseline characteristics

Characteristic	Randomized women (n = 285)	P value ^a	Randomized women with complete dataset (n = 176)	P value ^b	Total population in NFIR (n = 28 873)
Age	52 (29-91)	.57	50 (29-91)	.61	51 (17-98)
Body mass index	26 (19-47)	.47	26 (20-47)	.23	26 (15-85)
Preoperative cough-jump stress test (g)	35 (0-274)	.81	31 (0-274)	.36	36 (0-500)
Preoperative post-void residual urine (mL)	2 (0-150)	.95	2 (0-80)	.28	2.0 (0-500)
Preoperative maximum urinary flow rate (mL/s)	28 (0-50)	.87	29 (0-50)	.37	28 (0-50)
Postoperative cough-jump stress test (g)	0 (0-203)	.47	0 (0-135)	.72	0 (0-300)
Postoperative post-void residual urine (mL)	5 (0-300)	.87	5 (0-140)	.52	5 (0-500)
Postoperative maximum flow rate (mL/s)	20 (0-50)	.53	20 (0-50)	.61	21 (0-50)

Note: Data are given as median (range).

Mann-Whitney *U* test was used when analyzing continuous data.

Abbreviation: NFIR, The national Norwegian Female Incontinence Registry.

^aWomen randomized for validation compared with the total population in the NFIR.

^bWomen randomized for validation with complete datasets compared with the total population in the NFIR.

an AJUST™ sling procedure had been entered as either a retro-pubic TVT (n = 2) or a TVT-O procedure (n = 2) in the NFIR. For the registration of complications during and following the surgery, the kappa of 0.86 was somewhat lower than the other kappa values. Nevertheless, the observed agreement between the medical records and NFIR was 98.9%, with two cases that had complications reported to NFIR but that were not mentioned in the medical record, and one case with a complication not reported to the registry.

The ICC of the continuous variables validated are shown in Table 3. All variables had excellent agreement (ICC 0.94-1.00), indicating a strong measurement reliability between the patients' medical records and the NFIR. However, there were a high number of missing values in the pre- and postoperative maximum flow rates (28.1% and 35.8%, respectively) and in the postoperative cough-jump pad stress tests (11.9%). No difference in accuracy was found in high-volume hospitals compared with low-volume hospitals, nor did accuracy change over time (Table S1).

4 | DISCUSSION

The present validation study of the Norwegian Female Incontinence Registry revealed excellent accuracy for both continuous variables (ICC >0.94) and categorical variables (Cohen's kappa >0.86) when comparing the registry entries with the reference information in the patients' medical records. The completeness of the registry data also increased to almost complete coverage of all urinary incontinence surgeries performed in Norwegian public hospitals. A validation study of the Danish Urogynecology Database published in 2013

showed the same high completeness and accuracy as the present study.¹³

The value of a health registry largely depends on the quality of the contained data.⁶ Several distinct data quality attributes have been suggested,^{6,14-16} but many of them are overlapping or have different interpretations, sometimes based on ambiguous definitions. There is currently no established standard for which quality dimensions are to be used when assessing medical health registries. However, two frequently cited data quality attributes are data accuracy and completeness.¹⁴ According to Bray and Perkin, accuracy is defined as the proportion of cases within a dataset with a given characteristic that genuinely has that attribute.¹⁵ In the present study, we assessed data accuracy by comparing key variables selected for validation with the patients' medical records as reference, thereby assuming that the source data (patients' medical records) represent "true values" Reliability as opposed to accuracy, both being integrated in the validity dimension, relates to data reproducibility, not whether the data reflects the "true values".¹⁷ In the absence of a "true value" to determine the accuracy of the rating, inter-rater agreement and intraclass correlation were chosen as means of obtaining information on the accuracy of the ratings.

The completeness of a health registry is defined as the extent to which all cases in the target population are included.¹⁶ In our study, the completeness of the registry improved over time and now contains data from nearly all women undergoing incontinence surgery in Norway. Norway provides a public healthcare system for all inhabitants in which surgical treatment for urinary incontinence is treated free of charge. Therefore, only a few private hospitals in Norway perform incontinence surgeries each year. These hospitals only rarely report their surgeries to the NPR. As of 2019, only one private

FIGURE 2 The Norwegian Female Incontinence database completeness.¹The proportion of women with a correct urinary incontinence operation code registered both in the NFIR and the Norwegian National Patient Registry. *2008-2012: Completeness estimated comparing NFIR with NPR data only. 2013-2017: Completeness estimated comparing NFIR with both NPR data and the hospitals' local administrative systems

TABLE 2 Inter-rater agreement for non-continuous variables

Variable	n ^a	Missing (%) ^b	Observed agreement (%) ^c	Kappa (95% CI)
Type of SUI surgery performed	283	0.7	97.5	0.93 (0.88-0.98)
Complications yes/no	282	1.1	98.9	0.86 (0.71-1.00)
Treatment satisfaction ^d	278	2.5	98.6	0.95 (0.91-1.00)

Abbreviations: 95% CI, 95% confidence interval; SUI, stress urinary incontinence.

^aNumbers of valid cases.

^bPercentage of missing values in the registry.

^cObserved agreement calculated as concordant answers divided by n.

^dOrdinal data, estimates based on weighted Cohen's kappa.

hospital voluntarily reports its incontinence data to the NFIR. The women having their surgical treatment for incontinence at a private hospital would therefore not be detected in the comparison between NFIR and NPR. However, a phone survey with private clinics performed in 2019 revealed that less than 1% of the female incontinence surgeries are being performed annually at private hospitals.

There are several strengths in the present study. To investigate the accuracy of the NFIR, we used a comprehensive review of the patients' medical records, where the reviewers were blinded to the

previously stored information in the national registry. The number of cases included was well within the sample size calculations for kappa statistics and thus well powered for detecting robust estimates of the inter-rater agreement. Furthermore, the study population included women from almost every hospital reporting to the NFIR, minimizing the risk of self-selection bias which often hampers clinical studies and strengthening the generalizability of the findings.

A study limitation was that not all NFIR variables were assessed in the validation process. Although we found high accuracy of the

Variable	n ^a	Missing (%) ^b	ICC (95% CI)	Mean difference (95% CI) ^c
Time since surgery (d) ^d	282	1.1	1.00 (1.00-1.00)	-2.98 (-19.7 to 13.7)
Preoperative cough-jump stress test (g)	274	3.6	0.99 (0.98-0.99)	1.14 (0.63-1.65)
Preoperative post-void residual urine (mL)	264	7.3	0.94 (0.92-0.95)	0.57 (0.36-0.78)
Preoperative maximum urinary flow rate (mL/s)	205	28.1	0.97 (0.96-0.98)	0.61 (0.46-0.76)
Postoperative cough-jump stress test (g) ^e	251	11.9	0.95 (0.94-0.96)	0.64 (0.43-0.86)
Postoperative post-void residual urine (mL) ^e	267	6.3	0.95 (0.94-0.96)	0.52 (0.12-0.92)
Postoperative maximum flow rate (mL/s) ^e	183	35.8	0.98 (0.97-0.98)	-0.13 (-0.27 to 0.01)

^aNumbers of valid cases.

^bPercentage of missing values in the registry.

^cMean difference between the reviewer and the incontinence registry.

^dCalculated as the number of days since surgery and at the time of data analysis.

^e6-12 months postoperatively.

TABLE 3 Intraclass correlation coefficient for continuous variables

selected key variables, we can only assume that the other variables have the same degree of accuracy, as all of the data in the registry are collected and entered into the NFIR in the same manner. Another concern is the possibility of introducing typing errors during the re-extraction of the cases in the review process of the patients' medical records. Furthermore, the degree of missing values for a case in the registry may reduce the data quality accuracy, as the lack of information in the source data or ambiguous variable definition could potentially reduce the accuracy of a variable in the registry.¹⁵ However, missing values may also reflect non-optimal clinical examinations. In the present study, there were a high number of missing data in the pre- and postoperative maximum flow rates, and in the postoperative cough-jump pad stress tests. These tests are not mandatory, although recommended, and are done at the discretion of the examining doctor. To ensure that the missing values were not an indication of inadequate reporting to the registry but rather a result of these tests not having been performed, we compared and found a similar distribution of missing data in the registry and the patients' medical records. We therefore concluded that the missing data were due not to lack of reporting to NFIR but rather to the fact that some departments do not routinely perform flow rate analysis or postoperative cough-jump pad stress tests, likely in patients who report clinical postoperative success.

5 | CONCLUSION

The Norwegian Female Incontinence Registry is a reliable tool for quality assessment of incontinence surgery and research. The

registry completeness has improved over time and now contains data from nearly all women undergoing stress or mixed urinary incontinence surgery in Norway.

ACKNOWLEDGMENTS

Valuable help in statistical analysis was given by Statistician Jon Michael Gran. The authors also acknowledge the contributing members of the Norwegian Female Incontinence Registry at each reporting hospital department for their help in retrieving the source data for reference.

CONFLICT OF INTEREST

Sigurd Kulseng-Hanssen, Tomislav Dimoski and Rune Svenningsen hold part-time positions at the Norwegian Female Incontinence Registry. Rune Svenningsen has also received speaker fees from Astellas and Gedeon Richter. The authors declare no other conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Dyrkorn OA, Staff AC, Kulseng-Hanssen S, Dimoski T, Svenningsen R. The completeness and accuracy of the Norwegian Female Incontinence Registry. *Acta Obstet Gynecol Scand*. 2020;99:1618-1625. <https://doi.org/10.1111/aogs.13951>

PAPER III

Previous obstetrical history does not impact short-term mid-urethral sling outcomes

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Received: 16 January 2021 / Accepted: 2 May 2021
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Abstract

Introduction and hypothesis

Pregnancy and delivery are known risk factors for stress and mixed urinary incontinence. The most common surgical treatment is mid-urethral sling (MUS) surgery. This study evaluated the potential impact of the obstetrical history on the short-term subjective and objective failure rates after MUS surgery.

Methods

A registry-based surgical cohort study using data from the Medical Birth Registry of Norway (MBRN) and the national Norwegian Female Incontinence Registry (NFIR). Data from 14,787 women that underwent MUS surgery from 1998 to 2016 with complete registrations in the MBRN were included. Outcomes were 6–12-month postoperative subjective and objective failure rates. The potential impact of obstetrical and constitutional factors on both outcomes was tested in a multivariate logistic regression model.

Results

Several obstetrical variables seemed to impact both outcomes in the univariate analyses. However, in the multivariate analyses, none of the obstetrical variables significantly impacted subjective failure, and only being nulliparous before MUS surgery remained a risk factor for objective failure [aOR 1.60, (95% CI 1.07–2.40), $p = 0.022$]. High body mass index at time of surgery, non-retropubic slings, high preoperative urgency symptom load, and surgical complications were all strong risk factors for poor outcomes in the multivariate analyses.

Conclusion

Although childbirth is considered a risk factor for developing stress urinary incontinence, childbirth does not appear to affect the result of MUS in parous women. Our results suggest that nulliparous women with SUI may have a different pathophysiology than SUI after childbirth.

Keywords Stress urinary incontinence · Mid-urethral sling · Pregnancy · Obstetric delivery

Introduction

Female urinary incontinence (UI) is the most prevalent long-term pelvic floor disorder with a substantial negative impact on women's quality of life, productivity, socializing, and sexuality [1, 2]. Stress urinary incontinence (SUI), defined as involuntary loss of urine on physical exertion, sneezing, or coughing [3], affects approximately 15% of the female population, with the highest prevalence found in women between 25 and 49 years of age [1].

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Although the etiology of SUI is multifactorial, childbirth is uniformly considered a significant risk factor [4–7]. The underlying pathophysiology has not been entirely determined, but it has been proposed that pelvic floor injuries may weaken the supportive structures around the bladder neck and urethra through mechanical forces such as compression, stretching, or tearing of nerves, muscles, and/or connective tissue, causing SUI [8]. However, there is an ongoing debate regarding the possible long-term effects of pregnancy itself on later pelvic floor dysfunction and the additive effects of vaginal delivery in combination with other risk factors, such as birth weight, operative vaginal delivery and maternal age. There is also some evidence of a protective effect on pelvic floor function from cesarean delivery in the short term compared to vaginal delivery, but long-term protection has been questioned [4, 5, 9].

Surgical treatment is usually recommended when conservative treatment options fail [10]. Over the last decades, mid-urethral slings (MUS) have been established as the standard surgical treatment for SUI and stress-dominant mixed urinary incontinence (MUI) mainly due to their high efficacy, long-term durability, and lower rates of repeat surgery compared to other incontinence procedures [11]. Despite the high cure rates, there is still a group of women for whom the surgery fails in obtaining continence. Some of the risk factors identified are age at time of surgery, obesity, concomitant pelvic organ prolapse surgery, and surgical technique [12–16].

Even though childbirth is considered a significant risk factor for SUI development, we have to date little knowledge on whether the same obstetrical factors that caused injuries to the pelvic floor leading to SUI could potentially also determine the success of later SUI surgery. Norway has maintained national medical registries for many years. A national compulsory birth registry has been in place since 1967 and a national quality registry for female urinary incontinence surgery since 1998. Combining these two registries, we aimed to investigate the potential impact of various obstetrical factors on short-term subjective and objective failure rates after MUS surgery.

Materials and methods

This was a registry-based surgical cohort study of women recorded in the national Norwegian Female Incontinence Registry (NFIR) as having undergone MUS surgery for either stress or stress-dominant mixed urinary incontinence in Norway from 1998 to 2016. As the main aim of the study was to evaluate the impact from previous obstetrical history on surgical outcomes of later MUS operations, data on these women from the NFIR were then merged with data from the Medical Birth Registry of Norway (MBR) from its inception to 2016.

The Medical Birth Registry of Norway (MBRN) was established in 1967 as a mandatory population-based registry for all deliveries in Norway with nearly complete coverage. It receives notification of all deliveries in Norway with information on maternal health as well as prenatal, obstetrical, and neonatal outcomes.

The NFIR was established in 1998 and is a national quality registry for women undergoing urinary incontinence surgeries in Norway [17]. Participating is not mandatory, but > 95% of all female incontinence operations in Norway are performed in public hospitals that regularly report to the registry. The registry is used to improve the quality of incontinence surgeries at reporting hospitals by comparing results and complication rates to a national average in addition to collecting data for research. In recent years the registry has achieved almost complete coverage of women undergoing incontinence surgery and shown high reliability of reported and stored data [18]. Hospitals performing female incontinence surgery report their preoperative and 6–12-month postoperative subjective and objective data to NFIR. Subjective data are collected using a validated short-form urinary incontinence disease-specific questionnaire that calculates indices for the load of stress and urgency symptom bother [19]. The stress and urgency urinary incontinence indices are calculated from two domains of clustered questions and range from 0 to 12 (stress) and 0 to 8 (urgency), respectively. A high index score indicates a high symptom load with 0 indicating no symptoms. In addition, objective clinical data are reported by the surgeon at the time of the operation including results from preoperative objective testing, urodynamic findings, type of incontinence procedure, and any surgical complications occurring at or following surgery. Lastly, subjective and objective data from a mandatory follow-up 6–12 months after surgery are reported using the same validated questionnaire for subjective data as well as reporting results from objective testing, uroflowmetry, and post-void residual urine measurements. At the time of data extraction, 29 of the 39 hospital departments performing female incontinence surgery in Norway reported to the registry, which included approximately 70% of the incontinence surgeries performed in Norway during this time period (data given to authors from the NFIR).

The two outcomes for this study were short-term (6–12-month) subjective and objective SUI failure rates after primary MUS surgery. Patients with concomitant pelvic organ prolapse (POP) surgery or lacking information on whether the surgery was a primary or recurrent SUI operation were excluded. Subjective failure was defined as a stress urinary incontinence index score > 0 at the postoperative 6–12-month follow-up. Objective failure was defined as an increase in pad weight ≥ 1 g during a standardized cough-jump pad-weighing stress test consisting of 20 jumping jacks on the spot and three forceful coughs in the standing position with 300 ml bladder volume [20]. Women who were registered in the NFIR as

having undergone a later operation for recurrent SUI after previous MUS before the 6–12-month follow-up were defined as both subjective and objective failures in the statistical analyses.

From the NFIR, the following data were extracted: date of surgery, type of mid-urethral sling (retropubic, inside-out obturator, outside-in obturator, or mini-sling), body mass index (BMI) at time of surgery, preoperative post-void residual urine, preoperative maximum urinary flow rate, maximum urethra closure pressure, pre- and 6–12-month postoperative results from the cough-jump pad-weighting stress tests, pre- and 6–12-month postoperative stress, and urgency urinary incontinence indices and complications (yes/no) during or immediately after surgery (complete list of complications provided in supplemental Appendix 1).

From the MBRN, the following data were extracted: parity, mode of delivery, offspring birth weight, head circumference, presentation, episiotomy, grade 3 and 4 perineal tears, and mothers' age at delivery. In addition, time from last delivery until MUS surgery was calculated. To ensure complete data from the birth registry and accurately determine which women were nulliparous at the time of surgery, we chose to exclude women born before 1949 as these could theoretically have given birth to non-registered children before the inception of the MBRN.

Potential obstetrical and constitutional risk factors were tested against both subjective and objective failure as previously defined, using a multivariate logistic regression model. The risk factors evaluated in the model were parity (0, 1, 2, or ≥ 3), mode of delivery, presentation, episiotomy (yes/no), offspring birth weight ($<$ or ≥ 4000 g), head circumference ($<$ or ≥ 36 cm), perineal tear grade 3 or 4 (yes/no), age at first delivery ($<$ or ≥ 25 years), age at surgery (in decades), BMI at surgery (normal weight: 18.5–24.9, overweight: 25.0–29.9, and obese: ≥ 30.0 as defined by the World Health Organization), time from last delivery until surgery (in decades), preoperative stress and urgency urinary incontinence index scores (in quartiles), preoperative cough-jump pad-weighting stress test results (in quartiles), preoperative post-void residual urine ($<$ or ≥ 100 ml), preoperative maximum urinary flow rate ($<$ or ≥ 15 ml/s), type of mid-urethral sling (4 groups), and surgical complications (yes/no). Fetal macrosomia, defined as ≥ 4000 g, was used as a dichotomization of birth weight. Head circumference and age at first delivery were dichotomized around the median. Mode of delivery was stratified in three groups (spontaneous vaginal only, instrumental vaginal, cesarean only). Women who had at least one instrumental vaginal delivery were stratified to the instrumental vaginal delivery group regardless of whether they had also had cesarean or spontaneous vaginal deliveries. Women stratified to the cesarean group had only had cesarean deliveries.

Methods, definitions, and units in the study conform to the standards recommended by the International

Urogynecological Association and International Continence Society joint report on the terminology for female pelvic floor dysfunction [3].

The study was approved by the Regional Committee for Medical and Health Research Ethics in Norway (#2015/434) and the Institutional Personal Data Officer at Oslo University Hospital. Exemption from the requirement for patient consent was given because there was no foreseen risk of violation of personal data in the study combined with the need for completeness of data for study validity. Full anonymity of participating women was maintained in the final study file used for data analysis. The study was registered at [ClinicalTrials.gov](https://www.clinicaltrials.gov/ct2/show/study?term=NCT02999347) (NCT02999347).

Statistical analyses were performed using STATA: Software for Statistics and Data Science version 16.0 (StataCorp). Continuous variables are presented as medians with interquartile range (IQR), and dichotomous variables are presented as frequencies (percentages). Mann-Whitney U-test was used to compare continuous variables and Fisher's exact test for dichotomous variables. Potential risk factors for objective or subjective short-term failure after MUS are presented as crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) and *p*-values in the logistic regression model. A significance level of 5% was used. Covariates with a significance level of 0.20 in the univariate crude analysis were included in the multivariate regression model. A backward variable selection was then used by stepwise removal of variables with significance levels > 0.05 . No significant interactions were found between the independent variables. The final model was tested using a goodness-of-fit test (Hosmer-Lemeshow).

Results

After merging data from the Norwegian Incontinence Registry and the Medical Birth Registry of Norway, 18,027 women from 29 reporting departments who had undergone a mid-urethral sling (MUS) procedure were found eligible for inclusion (Fig. 1). Women with duplicate records, those who had undergone non-MUS surgery for their stress urinary incontinence (SUI) or those who lacked information regarding this being their primary operation or an operation for recurrent SUI were excluded. The remaining 14,787 women were included in the study analyses, of which 14,171 (96%) had undergone at least one childbirth and 616 (4%) were nulliparous before their primary MUS procedure (Fig. 1).

Baseline clinical characteristics and short-term (6–12-month) subjective and objective failure rates for both parous and nulliparous women are presented in Table 1. The median age was 47 years (IQR: 42–52) and median BMI 25.4 kg/m² (IQR: 23.0–29.0) for the total study group. For parous women, the median time from last delivery until MUS operation was

Fig. 1 Flowchart

14 years (IQR: 0–46). Additional obstetrical descriptive factors such as parity, age at first delivery, presentation, maximum birth weight, episiotomy, perineal tear grade 3/4, and mode of delivery are presented in Table 1.

Retropubic MUS was the most common sling type utilized (78.4%). For the total population, the subjective and objective 6–12-month failure rate was 28.9% and 7.7%, respectively (Table 1).

In the non-parametric analysis, nulliparous women had a significantly higher subjective and objective short-term failure rate compared with parous woman (subjective failure in 33.8% vs. 28.7%, $p = 0.010$ and objective failure in: 10.3% vs. 7.6%, $p = 0.036$) (Table 1). However, at baseline, the nulliparous women were significantly older ($p < 0.001$), had a higher BMI ($p < 0.001$), and had a higher preoperative symptom load for both stress and urgency urinary incontinence reflected by their higher preoperative stress and urgency urinary incontinence symptom scores ($p < 0.001$) (Table 1).

In the univariate analysis, being nulliparous also seemed to impact both subjective and objective failure

rates [OR 1.27 (95% CI 1.05–1.53), $p = 0.012$, and 1.41 (95% CI 1.02–1.95), $p = 0.037$] (Tables 2 and 3). Additional obstetrical factors seemingly impacting failure rates in the univariate analyses were head circumference (subjective failure), age at first delivery (objective failure), and time from last delivery until surgery (objective failure) (Tables 2 and 3). In the multivariate analyses, however, the only obstetrical factor significantly impacting the short-term objective failure rate was being nulliparous before MUS surgery, with an increased risk of 60% [aOR 1.60 (95% CI 1.07–2.40), $p = 0.022$] when compared with parous women having a median of two deliveries (Table 3). For subjective failure, none of the obstetrical factors investigated exerted any significant impact (Table 2). Constitutional factors that were significantly associated with the subjective and/or objective failure rate in the adjusted regression analyses included BMI at time of surgery, preoperative cough-jump stress test results, preoperative stress and urgency symptom loads expressed as preoperative stress and urgency urinary

Table 1 Baseline clinical characteristics, type of surgery, and failure rates (subjective and objective) 6–12 months after MUS for the study groups

Characteristic	All participants (<i>n</i> =14,787)	Para>0 (<i>n</i> =14,171)	Para=0 (<i>n</i> =616)	<i>p</i> ^a
Age at primary MUS (years)	47 (42–52)	47 (42–52)	50 (44–54)	< 0.001
BMI at primary MUS (kg/m ²)	25.4 (23.0–29.0)	25.4 (23.0–28.7)	27.1 (24.0–30.8)	< 0.001
Preoperative stress urinary incontinence index score ^b	8 (7–10)	8 (7–10)	9 (7–10)	< 0.001
Preoperative urgency urinary incontinence index score ^c	3 (2–5)	3 (2–5)	4 (2–6)	< 0.001
Preoperative cough-jump stress test (g)	33 (0–400)	33 (0–400)	33 (0–300)	0.079
Preoperative maximum urinary flow rate (ml/s)	29 (4–50)	29 (4–50)	27 (6–50)	0.064
Preoperative post-void residual urine (ml)	2 (0–483)	2 (0–483)	1 (0–230)	0.216
Preoperative MUCP ^d < 20 cmH ₂ O	1.8% (107/5808)	1.8% (99/5546)	3.1% (8/262)	0.151
Type of mid-urethral sling				
Retropubic	78.4% (11,599/14,787)	78.5% (11,126/14,171)	76.8% (473/616)	0.317
Inside-out obturator	13.5% (1999/14,787)	13.4% (1898/14,171)	14.9% (92/616)	0.277
Outside-in obturator	4.4% (652/14,787)	4.4% (628/14,171)	3.9% (24/616)	0.609
Mini-sling	3.7% (546/14,787)	3.7 (519/14,171)	4.4 (27/616)	0.330
Objective failure rate ^e	7.7% (832/10,843)	7.6% (786/10,398)	10.3% (46/445)	0.036
Subjective failure rate ^f	28.9% (3813/13,205)	28.7% (3630/12,664)	33.8% (183/541)	0.010
Time from last delivery until MUS (years)		14 (0–46)		
Parity		2 (1–9)		
Age at first delivery (years)		24 (14–44)		
Maximum birth weight (g)		3820 (770–5680)		
Normal cephalic presentation		88.7% (12,211/13,767)		
Breech presentation		6.9% (949/13,767)		
Abnormal cephalic presentation		4.4% (607/13,767)		
Episiotomy		8.6% (1188/13,767)		
Instrumental vaginal delivery		15.3% (2108/13,767)		
Perineal tear grade 3 or 4		5.4% (746/13,767)		
Cesarean delivery only		2.9% (404/14,171)		

Data are median (25th–75th interquartile range) or % (number/total) unless otherwise specified

Mann-Whitney U test was used when analyzing continuous data; Fisher exact test was used for categorical variables

Entries presented in bold indicates statistically significance (*p* < 0.05)

MUS mid-urethral slings, BMI body mass index

^a Para > 0 vs. Para = 0

^b Stress urinary incontinence index score is calculated from the validated NFIR questionnaire with range 0–12

^c Urgency urinary incontinence index score is calculated from the validated NFIR questionnaire with range 0–8

^d Maximum urethra closure pressure

^e Objective failure defined as 0-g leakage on a cough/jump pad weighing test

^f Subjective failure defined as stress urinary incontinence index score = 0

incontinence index scores, preoperative low maximum urinary flow rate, type of sling utilized, and surgical complications (Tables 2 and 3).

Discussion

This nationwide prospective cohort study based on high-quality registry data investigated the potential impact of women's obstetrical history expressed as various obstetrical factors on short-term subjective and objective failure rates after MUS surgery. The

results initially indicated that several obstetrical variables might exert an impact on both outcomes as shown in the univariate analyses. However, in the final multivariate model when adjusting for known constitutional factors, none of the obstetrical variables remained independent risk factors for subjective failure. Only nulliparity before MUS surgery remained an independent risk factor for objective failure. Risk factors such as high BMI at time of surgery, a high preoperative degree of objective leakage, a high preoperative symptom load for both stress and urgency symptoms, preoperative maximum urinary flow rate < 15 ml/s, type of sling utilized and surgical complications, however,

Table 2 Obstetrical and constitutional risk factors for subjective failure 6–12 months after MUS for the study group ($n = 14,787$)

Obstetric and constitutional variables	Subjective failure % (N) ^a	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
Parity					
0	33.8 (183/541)	1.27 (1.05–1.53)	0.012	1.18 (0.94–1.47)	*0.148
1	29.9 (472/1579)	1.06 (0.94–1.20)	0.350	0.95 (0.81–1.12)	0.550
2	28.7 (1742/6074)	Reference		Reference	
≥ 3	28.2 (1415/5011)	0.98 (0.90–1.06)	0.595	0.98 (0.88–1.09)	0.697
Vaginal delivery					
Cesarean delivery only	30.4 (123/404)	1.09 (0.87–1.37)	0.470		
Spontaneous	28.4 (3056/10,762)	Reference			
Instrumental	30.2 (574/1902)	1.09 (0.98–1.21)	0.113		
Presentation					
Normal cephalic	28.5 (3198/11,218)	Reference			
Abnormal cephalic	31.2 (177/597)	1.14 (0.95–1.37)	0.164		
Breech	29.0 (255/879)	1.03 (0.89–1.19)	0.751		
Episiotomy					
No	28.4 (3320/11,597)	Reference			
Yes	30.2 (310/1067)	1.02 (0.89–1.17)	0.769		
Birth weight (g)					
< 4000	29.2 (2374/8119)	Reference			
≥ 4000	27.6 (1255/4544)	0.92 (0.85–1.01)	0.053		
Head circumference (cm)					
< 36	29.8 (1302/4367)	Reference		Reference	
≥ 36	27.8 (2059/7410)	0.91 (0.83–0.98)	0.019	0.95 (0.86–1.05)	0.292
Perineal tear 3 or 4					
No	28.7 (3438/11,993)	Reference			
Yes	28.6 (192/671)	1.00 (0.84–1.19)	0.977		
Age at first delivery (years)					
< 25	28.9 (1884/6525)	Reference			
≥ 25	28.4 (1746/6139)	0.98 (0.91–1.06)	0.591		
Age at surgery (years)					
< 30	40.1 (27/66)	1.76 (1.07–2.89)	0.025	1.60 (0.87–2.96)	0.129
30–39	29.0 (583/2008)	1.04 (0.93–1.16)	0.494	1.09 (0.95–1.24)	0.231
40–49	28.2 (1796/6359)	Reference		Reference	
50–59	29.4 (1211/4125)	1.06 (0.97–1.15)	0.218	1.01 (0.90–1.13)	0.909
60–67	30.2 (195/646)	1.10 (0.92–1.31)	0.297	1.12 (0.86–1.44)	0.402
BMI at surgery (kg/m ²)					
< 25 (<i>normal</i>)	24.5 (1141/4666)	Reference		Reference	
25–29.9 (<i>overweight</i>)	29.9 (1066/3570)	1.32 (1.19–1.45)	< 0.001	1.25 (1.12–1.39)	< 0.001
≥ 30 (<i>obese</i>)	36.1 (706/1958)	1.74 (1.56–1.95)	< 0.001	1.54 (1.36–1.75)	< 0.001
Time from last delivery until surgery (years)					
0–9	27.9 (1081/3875)	0.93 (0.85–1.02)	0.156		
10–19	29.3 (1391/4750)	Reference			
20–29	28.6 (831/2902)	0.97 (0.88–1.07)	0.544		
≥ 30	28.9 (321/1109)	0.98 (0.85–1.13)	0.823		
Preoperative stress urinary incontinence index score ^b					
≤ 6 (< 25th percentile)	22.1 (529/2392)	Reference		Reference	
7–10 (25th–75th percentile)	29.2 (2502/8583)	1.45 (1.30–1.61)	< 0.001	1.22 (1.07–1.38)	0.003
11–12 (> 75th percentile)	37.4 (553/1478)	2.11 (1.82–2.43)	< 0.001	1.42 (1.17–1.72)	< 0.001
Preoperative cough-jump stress test (g)					
≤ 13 (< 25th percentile)	28.0 (898/3207)	Reference		Reference	

Table 2 (continued)

Obstetric and constitutional variables	Subjective failure % (N) ^a	Crude OR (95% CI)	<i>p</i>	Adjusted OR (95% CI)	<i>p</i>
14–67 (25th–75th percentile)	28.2 (1892/6704)	1.01 (0.92–1.11)	0.819	0.98 (0.87–1.11)	0.786
68–482 (> 75th percentile)	31.0 (1016/3281)	1.15 (1.04–1.28)	0.009	1.04 (0.91–1.71)	0.528
Preoperative urgency urinary incontinence index score ^c					
0–1 (< 25th percentile)	21.8 (1192/5476)	Reference		Reference	
2–5 (25th–75th percentile)	30.1 (1217/4049)	1.62 (1.46–1.78)	< 0.001	1.57 (1.39–1.78)	< 0.001
6–8 (> 75th percentile)	38.9 (1349/3469)	2.99 (2.65–3.39)	< 0.001	2.48 (2.10–2.93)	< 0.001
Preoperative post-void residual urine (ml)					
< 100	28.9 (3759/13,028)	Reference			
> 100	31.2 (49/157)	1.12 (0.80–1.57)	0.517		
Preoperative maximum urinary flow rate (ml/s)					
≥ 15	28.1 (2982/10,626)	Reference			
< 15	31.5 (123/391)	1.18 (0.95–1.46)	0.143		
Type of mid-urethral sling					
Retropubic	28.0 (2915/10,431)	Reference			
Inside-out obturator	32.4 (556/1717)	1.23 (1.11–1.38)	< 0.001	1.18 (1.03–1.35)	0.021
Outside-in obturator	30.2 (171/566)	1.12 (0.93–1.34)	0.243	1.26 (1.01–1.58)	0.043
Mini-sling	34.8 (171/491)	1.38 (1.14–1.67)	< 0.001	1.58 (1.24–2.01)	< 0.001
Surgical complications					
No	28.2 (3163/11,2236)	Reference			
Yes	33.0 (650/1969)	1.26 (1.14–1.39)	< 0.001	1.26 (1.10–1.43)	< 0.001

Data are n (%) unless otherwise specified

Entries presented in bold indicates statistically significance ($p < 0.05$)

OR odds ratio, CI confidence interval, MUS mid-urethral sling, BMI body mass index

^a Postoperative stress urinary incontinence index score > 0

^b Stress urinary index score is calculated from the validated NFIR questionnaire with range 0–12

^c Urgency urinary index score is calculated from the validated NFIR questionnaire with range 0–8

* Not adjusted for obstetrical factors

remained strong risk factors for both subjective and objective outcomes in the multivariate model. These constitutional risk factors for SUI have previously been well documented in the literature [11, 16, 21, 22].

Childbearing is identified as an important independent risk factor for SUI. In a large cross-sectional study including 27,900 women in Norway, SUI prevalence was associated with increasing parity, with a relative risk of 1.9 (95% CI, 1.6–2.2) for primiparous women and 2.3 (95% CI, 2.0–2.6) for women with two deliveries [6]. The association between childbearing and urinary incontinence is, however, not fully understood. Data suggest that pregnancy and delivery induce pelvic floor injury through mechanical forces [8], causing increased bladder neck hypermobility and decreased pelvic floor contractility [23, 24]. Parous women have an attributable risk of 50% for SUI development related to pregnancy and childbirth [9]. Furthermore, several studies have shown that vaginal delivery is a significant risk factor for the development of SUI [4, 5, 9, 25].

However, to date it is unknown whether these obstetrical factors such as delivery mode, obstetric anal sphincter injury,

levator ani avulsion, and fetal factors also impact surgical outcomes in women with SUI. Parity is, to our knowledge, the only obstetrical factor previously studied [13, 15]. Laterza et al. evaluated the effect of parity at the time of surgery on short- and long-term outcomes in women who underwent SUI surgery by MUS [15]. This study utilized data from a previously published randomized controlled trial that included 554 patients in which subjective and objective outcomes of TVT and TVT-O were compared. They found no significant association between parity and the risk of either subjective or objective SUI recurrence. Furthermore, in a prospective cohort study by Majkusiak and co-workers including 238 women who had a retropubic MUS operation, the number of vaginal deliveries showed no impact on short-term sling failure [13]. Thus, the findings of both of these studies are consistent with the results in the present study. However, as we had the possibility of also including a sufficiently large group of women who had not given birth before their MUS operation, we were able to demonstrate that being nulliparous before MUS surgery seems to be an independent risk factor for objective

Table 3 Obstetrical and constitutional risk factors for objective failure 6–12 months after MUS for the study group ($n = 14,787$)

Obstetric and constitutional variables	Objective failure % (N) ^a	Crude OR (95% CI)	<i>p</i>	Adjusted OR (95% CI)	<i>p</i>
Parity					
0	10.3 (46/445)	1.41 (1.02–1.95)	0.037	1.60 (1.07–2.40)	*0.022
1	7.8 (102/1305)	1.03 (0.83–1.30)	0.754	1.11 (0.81–1.53)	0.568
2	7.6 (380/5028)	Reference		Reference	
≥3	7.5 (304/4065)	0.99 (0.85–1.16)	0.887	0.93 (0.74–1.18)	0.568
Vaginal delivery					
Cesarean delivery only	7.8 (23/295)	1.04 (0.67–1.59)	0.876		
Spontaneous	7.7 (680/8809)	Reference			
Instrumental	6.7 (106/1589)	0.85 (0.69–1.06)	0.146		
Presentation					
Normal cephalic	7.6 (696/9203)	Reference			
Abnormal cephalic	7.1 (32/450)	0.94 (0.65–1.35)	0.723		
Breech	7.8 (58/745)	1.03 (0.78–1.36)	0.825		
Episiotomy					
No	7.6 (722/9542)	Reference			
Yes	7.5 (64/856)	0.99 (0.76–1.29)	0.924		
Birth weight (g)					
< 4000	7.7 (511/6651)	Reference			
≥ 4000	7.3 (275/3746)	0.95 (0.82–1.11)	0.527		
Head circumference (cm)					
< 36	7.4 (268/3624)	Reference			
≥ 36	7.2 (435/6037)	0.97 (0.83–1.14)	0.728		
Perineal tear 3 or 4					
No	7.6 (743/9841)	Reference			
Yes	7.7 (43/557)	1.02 (0.74–1.41)	0.883		
Age at first delivery (years)					
< 25	8.3 (436/5239)	Reference		Reference	
≥ 25	6.7 (350/5159)	0.80 (0.69–0.93)	0.003	0.97 (0.76–1.25)	0.819
Age at surgery (years)					
< 30	10.2 (6/59)	1.48 (0.63–3.46)	0.370	1.72 (0.58–5.1)	0.328
30–39	7.8 (132/1696)	1.10 (0.90–1.35)	0.364	1.03 (0.74–1.43)	0.866
40–49	7.1 (369/5181)	Reference		Reference	
50–59	8.4 (288/3414)	1.20 (1.02–1.41)	0.025	1.02 (0.74–1.40)	0.898
60–67	7.3 (36/492)	1.03 (0.72–1.47)	0.873	0.73 (0.40–1.35)	0.305
BMI at surgery (kg/m ²)					
< 25 (<i>normal</i>)	5.7 (214/3781)	Reference		Reference	
25–29.9 (<i>overweight</i>)	7.1 (205/2882)	1.28 (1.05–1.56)	0.016	1.21 (0.95–1.53)	0.114
≥ 30 (<i>obese</i>)	9.8 (154/1575)	1.81 (1.46–2.24)	< 0.001	1.48 (1.13–1.93)	0.004
Time from last delivery until surgery (years)					
0–9	7.3 (235/3241)	1.06 (0.89–1.27)	0.519	1.22 (0.90–1.65)	0.207
10–19	6.9 (267/3893)	Reference		Reference	
20–29	8.5 (201/2372)	1.26 (1.04–1.52)	0.019	1.00 (0.71–1.39)	0.981
≥ 30	9.5 (83/870)	1.43 (1.11–1.85)	0.006	1.61 (0.99–2.62)	0.056
Preoperative stress urinary incontinence index score ^b					
≤ 6 (< 25 percentile)	6.6 (127/1921)	Reference		Reference	
7–10 (25th–75th percentile)	7.4 (524/7111)	1.12 (0.92–1.37)	0.255	1.02 (0.77–1.36)	0.880
11–12 (> 75th percentile)	10.6 (129/1220)	1.67 (1.29–2.16)	< 0.001	1.04 (0.70–1.55)	0.856
Preoperative cough-jump stress test (g)					
≤ 13 (< 25th percentile)	5.7 (141/2488)	Reference		Reference	

Table 3 (continued)

Obstetric and constitutional variables	Objective failure % (N) ^a	Crude OR (95% CI)	<i>p</i>	Adjusted OR (95% CI)	<i>p</i>
14–67 (25th–75th percentile)	7.1 (393/5513)	1.28 (1.05–1.56)	0.016	1.30 (0.96–1.74)	0.095
68–482 (> 75th percentile)	10.4 (296/2837)	1.94 (1.58–2.39)	< 0.001	1.96 (1.43–2.68)	< 0.001
Preoperative urgency urinary incontinence index score ^c					
0–1 (< 25th percentile)	6.1 (158/2612)	Reference		Reference	
2–5 (25th–75th percentile)	7.2 (464/6437)	1.21 (1.00–1.45)	0.049	1.19 (0.91–1.57)	0.197
6–8 (> 75th percentile)	11.9 (194/1637)	2.09 (1.68–2.60)	< 0.001	1.89 (1.34–2.67)	< 0.001
Preoperative post-void residual urine (ml)					
< 100	7.6 (815/10,693)	Reference			
> 100	10.4 (14/135)	1.40 (0.80–2.45)	0.235		
Preoperative maximum urinary flow rate (ml/s)					
≥ 15	6.5 (563/8719)	Reference			
< 15	10.4 (33/317)	1.68 (1.16–2.44)	0.006	1.67 (1.09–2.57)	0.018
Type of mid-urethral sling					
Retropubic	6.8 (578/8539)	Reference			
Inside-out obturator	10.4 (151/1446)	1.61 (1.33–1.94)	< 0.001	1.90 (1.47–2.4)	< 0.001
Outside-in obturator	13.5 (59/436)	2.16 (1.62–2.87)	< 0.001	2.71 (1.87–3.92)	< 0.001
Mini-sling	10.4 (44/422)	1.60 (1.16–2.12)	0.004	1.63 (1.02–2.58)	0.040
Surgical complications					
No	7.5 (687/9219)	Reference			
Yes	8.9 (144/1623)	1.21 (1.00–1.46)	0.048	1.36 (1.03–1.80)	0.028

Data are *n* (%) unless otherwise specified

Entries presented in bold indicates statistically significance (*p* < 0.05)

OR odds ratio, CI confidence interval, MUS mid-urethral sling, BMI body mass index

^a Postoperative cough-jump pad-weighing test = 0 g

^b Stress urinary incontinence index score is calculated from the validated NFIR questionnaire with range 0–12

^c Urgency urinary incontinence index score is calculated from the validated NFIR questionnaire with range 0–8

* Not adjusted for obstetrical factors

failure compared with parous women, even after adjusting for obstetrical and known constitutional risk factors. We know from published literature that even though childbirth is a risk factor for stress urinary incontinence, studies have also demonstrated that stress urinary incontinence occurs in approximately 5%–11% of nulliparous women 25–64 years old [6, 26]. It is reasonable, therefore, to hypothesize that nulliparous women with SUI might have a different or additional underlying pathophysiological mechanism for their incontinence rather than a simple urethral hypermobility caused by trauma to the pelvic floor. In the present study, the nulliparous women had a higher BMI, which by itself is a known risk factor for SUI [16]. There is also evidence that hereditary factors could play a part, such as a different connective tissue composition in nulliparous women with increased risk of developing SUI. This was demonstrated in a study from Keane et al. which found significantly less periurethral collagen in nulliparous women with pure SUI compared to continent nulliparous controls, indicating a genetically higher susceptibility to SUI development [27]. Other potential explanations for SUI developing in nulliparous women with no

known trauma to the pelvic floor could include a poor sphincter function of unknown cause, a dysfunctional pelvic floor due to age-related atrophy of muscles, and/or undiagnosed neurological diseases. It has been demonstrated that women with sphincter insufficiency have lower cure rates after MUS compared to women with urethral hypermobility [12].

Constitutional factors were confirmed in this study as strong risk factors for both subjective and objective short-term failure. In population-based studies high BMI has proved to be one of the main risk factors for both the development of stress urinary incontinence [28] and poor outcomes after MUS [16]. Retropubic MUS are considered to be more effective than trans-obturator and mini-slings [11]. This was also confirmed in our study demonstrating a significantly lower failure rate when retropubic MUS was utilized. A high preoperative urgency symptom load almost doubled the odds of subjective and objective failure after MUS surgery in our study, which is in agreement with previous published studies [21, 22]. Several studies have also found advancing age to be a risk factor for MUS failure [14, 21, 29]. In our study, age at surgery was not a risk factor for subjective or objective

failure. However, we believe the reason for this are that women > 67 years (born before 1949) were excluded from our study as these could theoretically have given birth to non-registered children before the inception of the MBRN. In a study by Engen et al., also based on data from approximately the same cohort of women, it was demonstrated that a significant increase in MUS failure only occurred for women in the 7th decade and older [29].

This study's main strength was the use of data from a large population-based cohort. The cohort was identified through a surgical incontinence registry with proven high coverage and data reliability [18]. All inhabitants in Norway are provided with a public healthcare system where surgical treatment for urinary incontinence is free of charge. This ensured a low degree of selection bias and a high degree of statistical precision in the analysis. Consequently, we believe the present study has a high level of external validity. Furthermore, we were also able to explore the women's obstetrical history in detail because of the merging with data from the Medical Birth Registry of Norway (MBRN), which has been proven suitable for population-based studies [30].

There are also several important limitations to this study, the most important being that we were only able to study the potential impact of obstetrical factors on short-term results, as the NFIR only has high coverage for the first postoperative 6–12 months of follow-up. Later follow-ups are optional for the reporting hospitals and were therefore deemed to have a too high risk of selection bias to be used in the present study. We realize that a potential impact from obstetrical factors on long-term results therefore cannot be ruled out with certainty based on our study. Other important limitations to this study were the inability to adjust for factors related to the surgeon's experience (surgical volume), local differences in incontinence assessment, and local preferences regarding the type of sling. Furthermore, all use of registry data carries the risk of missing data and inaccuracy in the individual entries, potentially impacting the results, and should always be interpreted with that in mind.

Knowledge about factors associated with treatment failure is essential when counseling patients regarding MUS surgery's efficacy and to facilitate appropriate expectations of women with SUI women prior to their decision on surgery. Although pregnancy and childbirth are considered significant risk factors for developing stress urinary incontinence, these obstetrical factors do not seem to majorly impact the short-term surgical results. However, the negative impact on objective failure rates of being nulliparous before MUS surgery calls for further research to fully understand the mechanism behind the development of SUI in this sub-group of women.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00192-021-04836-5>.

Acknowledgments Valuable help in extracting data from the Norwegian Female Incontinence Registry (NFIR) was given by Tomislav Dimoski, system developer at the Norwegian National Female Incontinence Registry. The authors also acknowledge the help in statistical analysis given by statistician Jon Michael Gran.

Funding Open access funding provided by University of Oslo (incl Oslo University Hospital). The study was funded by Oslo University Hospital and supported by a grant from the Norwegian Medical Association (no. 14/1695). The funding sources had no role in the study design, data analysis, or writing of the report.

Declarations

Conflicts of interest Sigurd Kulseng-Hanssen and Rune Svenningsen hold part-time positions at the Norwegian Female Incontinence Registry. Rune Svenningsen has also received speaker fees from Astellas and Gedeon Richter. The authors declare no other conflicts of interest.

Conference presentations None.

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