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Complications of Vaginal Synthetic Sling Surgeries in Women: Population Based Cohort Study

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Surgery

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COMPLICATIONS OF VAGINAL SYNTHETIC SLING SURGERIES IN WOMEN
POPULATION BASED COHORT STUDY

Monograph Format

BY

AL-HOTHI, HANA'A

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The University of Western Ontario
London, Ontario, Canada

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Abstract

Synthetic sling surgery is the procedure of choice for surgical correction of stress urinary incontinence (SUI) in females. However, complications do occur, and may require surgical intervention to treat them in some instances. In a retrospective study we identified and analyzed those complications to determine their incidence and associated predictive factors. A total of 59,887 women who had synthetic sling procedure were included. Incidence of surgically treated complications was 2.2 % ((95% CI 2.07- 2.30) and at 10 years follow up cumulative incidence rate was 3.3% (95% CI 3.0- 3.5). There was no significant difference in complication rate between urologists versus gynecologists. A significant reduction in complications was noted with high surgical volume providers (HR 0.73, 95% CI 0.65-0.83). Patient' factors like age and simultaneous surgeries had significant effect. Results support the Food and Drug Administration recommendation about use of synthetic meshes and slings in vaginal surgery.

Keywords

Synthetic /mesh slings, Sling Revision, Stress Urinary Incontinence, Predictive Factors

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1 Introduction

Stress urinary incontinence (SUI) is considered a common condition in women with considerable socioeconomic impacts. Depending on its severity, therapeutic options differ. Surgical intervention with urethral slings is currently the procedure of choice for SUI correction in females (1). However, complications are well documented and necessitate removal or release some-times. In this thesis, we will demonstrate the results of a retrospective study in which the incidence of SUI surgery in women was measured and rate of surgically treated post sling complications were documented. Factors that might influence complications were also identified and discussed in view of statistics and literatures.

1.1 Stress Urinary Incontinence (SUI) in females

Stress urinary incontinence (SUI) in females is a common condition. It's considered to be symptom, sign and clinical disease. It is defined as "symptomatic complaint of involuntary leakage of urine on effort or exertion, and it can be noted in urodynamic study (UDS) as involuntary leakage of urine during increases in abdominal pressure in the absence of a detrusor contraction—so-called urodynamic stress incontinence" (2). Literature shows variable percentages of women affected by SUI, likely due to inconsistencies in definitions used by different investigators, which give a percentage between 15- 80% of women suffering from SUI (2).

1.1.1 Pathophysiology of SUI

Pathophysiology of SUI in females was studied and reviewed as early as 19th century (Sinclair AJ). At that time anatomic theories were postulated to understand and diagnose incontinence. Textbooks of that era reflected such opinions, and in an old gynecology book the author hypothesized that "the cause… is usually a prolapse of the anterior vaginal wall" and "incontinence is also of common occurrence" (3).

With advancement in technology and diagnostic tools in the early 20th century, a deeper understanding of pathophysiology of SUI was achieved and different theories evolved. The pressure transmission theory and sphincteric dysfunction theory were proposed and examined with repeated modifications over time (4). Currently, female SUI is thought to be the result of the combination of urethral hypermobility and intrinsic sphincteric dysfunction (ISD) (2). When intra-abdominal pressure increases due to cough or any other strenuous activity, the posterior wall of the urethra moves away from the anterior urethral wall. This causes opening of bladder neck due to urethral hypermobility, and leads to a loss of urine. ISD however, arises from defects within the urethra proper itself, so that the urethral sphincter is unable to close properly and generate enough resting urethral closing pressure to hold urine in the bladder (2).

1.1.2 Classification of SUI

Classification of SUI was proposed and modified by several investigators since 1920s (4). Blaivas and Olsson modified a classification system proposed by McGuire and colleagues (Table 1.1). This system was founded based on the position of the vesical neck in relation to symphysis pubis and it's descent during increase intra-abdominal pressure (diagnosed while imaging with fluoroscopy). It also monitors the integrity of the intrinsic sphincter mechanism (4).

Table 1.1 Classification of Urinary Incontinence by Blaivas and Olsson

Classification	Finding at Rest	Finding during Cough
Type 0	Flat bladder above symphysis pubis	Rotational descent of urethra and bladder base; no urine leakage
Type I	Flat bladder base above inferior margin of symphysis pubis	Bladder base descends less than 2 cm in relation to pubis; bladder neck and urethra both open with leakage
Type IIA	Flat bladder base above inferior margin of symphysis pubis	More then 2 cm descent of bladder and urethra below pubis; urethra open with leakage
Type IIB	Flat bladder base at or below inferior margin of symphysis pubis	More descent and rotation of bladder and urethra below pubis; urethra open widely with leakage
Type III	Bladder base rests above symphysis pubis; bladder neck and urethra are open	Bladder base above or below symphysis pubis; both bladder neck and urethra are open

1.1.3 Management of SUI

SUI has a significant life impact on patient in multiple aspects, and depending on the degree of incontinence and patient's coping strategies this impact can range between mild anxiety and fear of public activities to a full blown condition of depression and social isolation. Several areas of life can be affected such as social activities, physical performance and sports, sexual relationships, and even sleep may be affected (3). It is very important to consider and evaluate SUI impact on patient's life and follow it through out the treatment period.

Depending on severity of the condition, together with other patient factors, therapeutic options for SUI in women widely differ. Non-surgical intervention is well-established and recommended as first line therapy for urinary incontinence (UI) in form of behavioral (e.g. pelvic floor muscle rehabilitation) and pharmacological therapy (e.g. tricyclic antidepressant agent) (2). Such treatment modalities usually need high level of motivation and long-term commitment by patients. Surgical intervention aims to improve support to urethrovesical junction and strengthen all mechanisms contributing to continence. Different surgical methods have been described with variable success rates (2). Usually it's the surgeon' preference and training that play the most important role in choosing type of anti incontinence surgery. Other factors also contribute to the decision like the anatomical nature of incontinence and general health condition of the patients.

1.2 Sling Surgery for SUI

Urethral sling surgery is currently the procedure of choice for SUI with a variety of techniques and materials (2). It's routinely performed vaginally or abdominally (open or laparoscopic). In 2004, access through obturator foramen was described. Different materials have been consumed for sling fashioning, like autologous, allograft, xenograft, and synthetic materials.

1.2.1 History of Sling Surgery

Von Giordano first introduced the concept of sling surgery in 1907 as he used gracilis muscle graft wrapped around urethra (2). Frangenheim used rectus abdominis muscle and fascia in 1914, then, Millin adapted it for use in recurrent SUI (2). In 1933, Price used fascia lata to treat urinary incontinence in women with sacral agenesis, and he fixed it to the rectus muscle (5). Aldridge in 1940s described the use of paired strips of rectus fascia to form a sling and sutured them below the urethra (2). In 1970s, McGuire used the pubovaginal sling (PVS). He placed it at the bladder neck to correct urethral hypermobility and decrease the pressure transmission due to intra-abdominal pressure changes (2). First, it was used in patients who failed previous retropubic suspension procedures, and had a cure rate of 91%, which was why this procedure was reintroduced. Zaccharin in the 1960s and DeLancey in the 1990s hypothesized competing theories in which the role of pubourethral ligaments in maintaining urinary control was emphasized (2). They also stressed the role of midurethral mechanism in maintaining urinary continence under stress conditions (2). In 1990s,

Ulmsten described his midurethra theory, (previously known as integral theory), and it's first formulation was published in 1990 (6):

"For different reasons, stress and urge derive mainly from laxity in the vagina or it's supporting ligaments, a result of altered collagen/elastin"

Ulmsten postulated that injury due to different reasons such as surgery, aging, and parturition lead to weakening of the pubourethral ligaments. This affects the midurethral and anterior urethral wall support, which results in urinary incontinence (2). Radiological investigations later on provided a higher level of proof, and ultrasound technique brought a deeper understanding of vesicourethral dynamics after placement of sling (2) (6), which even further improved the understanding of continence mechanism in view of midurethra theory. Using those theories, the concept of mid urethral sling was developed, and since then, different approaches evolved with different materials and different suspension/fixation techniques.

1.2.2 Different Materials of Slings

Slings have been fashioned from various substances. A broad classification categorizes those substances to: autologous, allograft, xenograft, or synthetic materials. Ideally, sling material should be easily integrated into the host with the least tissue reaction, promote organized fibrosis, and be compatible with tissues (2).

Autologous slings were used in the late twenty-century. The most common material used currently is rectus fascia. A pronounced benefit of this type of

material is the lack of tissue reaction, which decrease risk of erosion significantly (7). Studies suggest that when autologous fascia is implanted there is a minimal to moderate inflammatory response, a moderate degree of collagen production, and a considerable degree of graft remodeling over the long term with reported rate of cure over 90% (7). However, such surgical approach increases operative time, prolongs recovery period post operatively with relative increase in pain, and limits the supply of the sling material. Also, the fact that another wound site is created for harvesting the sling adds to autologous disadvantages. Yet, they are considered to be the most successful biological material used in contemporary SUI surgery (7).

When allograft materials are used as SUI-slings, operative time decreases and the harvest wound is eliminated. Currently, allograft slings are derived from cadaveric fascia late or acellular human dermis. Before it' s implant, allografts undergo a long process of cleaning, sterilization and occasionally radiation to eradicate infective organisms and eliminate genetic materials before it is implanted (2) (7). Several studies evaluated changes in the mechanical properties of allografts after implantation, and results were mixed (7), however, histologic analysis revealed cadaveric dermis to have minimal host fibroblast infiltration and little neovascularity with marked thinning and degradation of the graft (2) (7). This may affect their long-term success rate. Another concern is low potential of disease transfer due to the low risk of erosion. There have been no cases reported yet of a disease transfer after allograft sling implantation, however, cases of HIV and Creutzfeldt-Jakob disease (CJD) transmission have been reported after transplantation of other cadaveric tissues (2). Although the risk of disease

transmission is low, human DNA has been detected in various allograft materials with an unknown clinical significance (2).

Xenograft has been used since the 1980s with less frequent use in recent years. Types available for use are porcine dermis or small intestinal submucosa (SIS) and bovine pericardium. As an allograft, xenograft tissue undergoes processing techniques in order to make it safer and more pliable (2). Sometimes, porcine dermis undergoes further crosslinking to make it more resistant to enzymatic digestion, and when laboratory studies evaluated mechanical properties and host response to xenograft different results were retrieved based on the material being cross-linked or not (7). Xenograft has significant lower tensile strength after implantation, and it has little or no inflammatory reaction, which results in subsequent limited collagen remodeling and graft degradation (2) (7). In a randomized multicenter clinical trial conducted to compare porcine xenograft sling, short autologous fascial sling and the synthetic tension free vaginal tape (TVT) in stress incontinence surgery, the re-operation rate for delayed failure of xenograft slings was significantly worse than both the TVT or fascia (8).

Synthetic slings were introduced for the first time in 1953 and were made of Nylon (2). Since then, range of synthetic materials have been used in SUI surgery with Gynecare TVT (Ethicon Women's Health & Urology, Somerville, NJ) being the first implantable mesh sling device, and it was composed of a polypropylene material (9). Synthetic slings have obvious advantages over all other types of slings: more uniform and consistent, more durable, unlimited supply of graft material in various sizes and shapes, and elimination of harvest sites, which consequently positively influences operative time and post operative pain and recovery. Also, the potential low

risk of disease transfer with biological materials is absent in the case of mesh. Regarding their mechanical properties, synthetic slings are greatly affected by the physical characteristics of the mesh, such as filament count, porosity, and polymer molecular weight (7).

In general, mesh stimulates a pronounced degree of inflammation, leading to massive cell infiltration and ultimate collagen production (2) (7). There is no degradation of the graft, and the mesh is usually completely infiltrated by the host tissue.

Significant differences exist between surgical meshes available today, such as type of material, amount of yarn, and amount of construction (10). Generally, they are classified into four classes depending on their pores size (Table 1.2).

Table 1.2 Amid Classification of Surgical Synthetic Materials

Type	Description	Brands
I	Pores > 75 µm Macroporous	Atrium, Trelex, Marlex, Prolene, Polypropylene
II	Pores < 10 µm Microporous	GORE-TEX, Surgical Membrane, Dualmesh
III	Macroporous with multifilamentous or microporous components	Teflon, Mersilene, Surgipro, MicroMesh
IV	Submicronic pore size	Silastic, Cellcard

This classification by Amid (1997) was used originally for synthetic materials in hernia surgery, and it's applied to urology as well (2). Type I mesh is totally macroporous, which facilitates its infiltration with macrophages, blood vessels, and collagen fibers. Type II includes materials

with pore size less than 10 µm. Type III includes prosthesis that is macroporous with multifilamentous or microporous components. Lastly, type IV includes materials with submicronic pore size (2). The most commonly used synthetic material for SUI slings is propylene mesh, which is composed of loosely woven strands with pore size greater than 80 µm. This allows movement of inflammatory cells during initial response and later on better host tissue ingrowth (2). Different types of synthetic slings available commercially are explained in Table 1.3.

Table 1.3 Synthetic Sling Different Materials

Trade Name	Composition	Details
Mersilene	Polyethylene terephthalate	Multifilament fibers, very porous, firmly embedded in native tissues
Teflon	Polytetrafluroethylene (PTEF)	Multifilament
GOR-TEX	Expanded PTFE	Very flexible
Silastic	Silicone plus woven polyethylene terephthalate	Minimal tissue reaction, easy removal or revision if necessary
ProteGen	Synthetic mesh with collagen matrix	Removed from market due to high rate of vaginal extrusion
Marlex, Prolene	Polypropylene	Monofilament with open-weave pattern

In spite all advantages of synthetic slings; serious disadvantages with variable occurrence rate do exist. Depending on physical properties of the mesh and the host inflammatory response, histological changes to the surrounding tissues occur, and might cause genitourinary erosion, vaginal extrusion or infection (2). Those disadvantages were noted to be more pronounced if synthetic sling was used as PVS, so it's not used for this surgery (2), and more commonly used in a midurethral positioning.

1.2.3 Surgical Approaches of Sling Surgery

Different surgical approaches have been described for synthetic sling. Choosing the specific approach is highly influenced by patient factors and criteria of her incontinence. One approach that is less commonly used currently is abdominal approach (5). It's used mainly when restrictions to lithotomy position cannot be overcome, or in the rare event of concurrent sling placement at the time of abdominal surgery. With this approach, the retropubic space is opened, with a tunnel created under bladder neck and proximal urethra, then, a sling is passed in that tunnel without vaginal incision and brought up to either Cooper's ligament or rectus fascia (5). The drawback of the abdominal approach is the risk of placing the sling too distally, which increases the risk of obstruction. Also, there might be a need to open the bladder to help in the dissection at the bladder neck level (5).

Abdomino-vaginal approach is more common than abdominal only approach (5). It has the advantage of simultaneous vaginal and abdominal repair when required. With this technique, accurate placement of the sling under bladder neck is achieved by dissecting both retropubic space and vaginal wall, with less dissection required retropubicly (5). Its benefits are markedly apparent in cases of recurrent SUI in which good access to both anterior vaginal wall and retropubic space is needed (5).

Vaginal approach is the commonest approach used for sling placement in SUI surgery. Both PVS and midurethral sling (MUS) are placed through this

access with help of special needles or introducers. Patient is placed in lithotomy position, and a longitudinal incision in the anterior vaginal wall is carried out at the level of bladder neck or midurethra. Depending on the SUI surgical kit, technique of placing and positioning sling differs. Initially, TVT was placed via a through vaginal incision through the retropubic space, (bottom-to-top approach). Later on, retropubic top-to-bottom approach has been introduced as the suprapubic arc system (SPARC, American Medical Systems, Inc., Minnetonka, MN, USA). (See Figure 1.1)

Then, a significant modification to the MUS insertion technique was introduced; the transobturator MUS (TMUS) was designed to avoid the blind passage of the needle through the retroperitoneal space (11). In this approach, needle traverses through obturator foramen for fixing the tape. First, it was inserted in an outside-in technique only, and then a second technique with an inside-out placement of the sling was described.

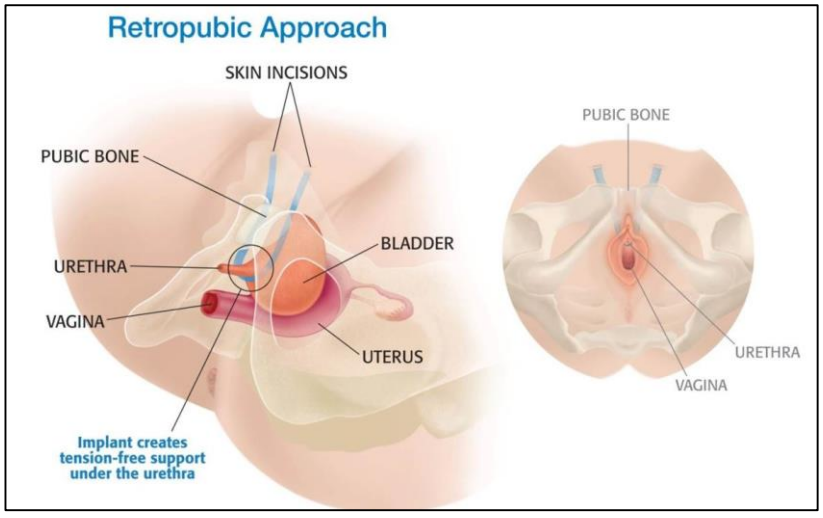

Figure 1.1 Vaginal approach in midurethral sling (MUS) placement via retropubic, bottom-to-top route.

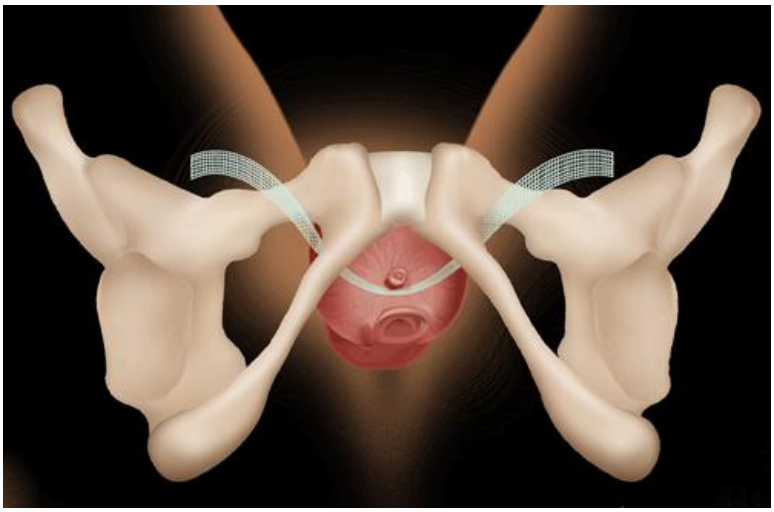

Figure 1.2 Vaginal approach of midurethral sling (MUS) Placement via transobturator route.

The vaginal approach continued to have modifications as new sling kits were developed and marketed. A single-incision sling was developed as a less invasive procedure with comparable subjective and objective cure rates in short term follow up. It may have a quicker recovery period and may have a lower risk of some complications; however, adverse effects like mesh erosion and urinary retention are not absent (11). Table 1.4 displays different surgical kits of slings available in the market with their surgical approaches and techniques.

Table 1.4 Commercial Synthetic Slings Kits

Name	Manufacturer	Technique/Approach
TVT	Ethicon	RMUS bottom to top
TVT-O	Ethicon	TMUS inside to out
TVT-Secure	Ethicon	Single incision
SPARC	AMS	RMUS top to bottom
Monarc	AMS	TMUS outside to in
MiniArc	AMS	Single incision

Name	Manufacturer	Technique/Approach
Advantage	Boston Scientific	RMUS bottom to top
Lynx	Boston Scientific	RMUS top to bottom
ObTryx	Boston Scientific	TMUS outside to in
Solyx	Boston Scientific	Single incision
Aris	Coloplast	TMUS outside to in
Ajust	Bard	Single incision (Adjustable sling)

1.3 Complications of Sling Surgery

As previously explained, there are different approaches and techniques of anti incontinence surgery using slings. Complications vary according to material and approaches.

As our study was to evaluate synthetic sling complications and potential risk factors, we will focus on complications of synthetic slings in subsequent discussion.

1.3.1 Classification of Synthetic Sling Complications

Complications in general can be classified to different groups and divisions depending on time of seeking medical advice, severity of complications, or site of occurrence of complications. Synthetic sling complications are significantly related to surgical approaches and/ or technique used in the surgery. Before we elaborate on such classification, we should display the

classification of the complications of meshes and tapes proposed by the International Urogynecological Association (IUGA) and the International Continence Society (ICS) Joint meeting in 2010. This classification aimed to be a basis for a registry of such complications and an aid to clinical practice and research (12). It categorizes the complications in relation to the insertion of prostheses and grafts in pelvic floor surgery in females, and it is based on category (C), time (T) and site (S) classes and divisions, in hopes of encompassing all possible scenarios for describing insertion complications and healing abnormalities of those surgeries. It uses numerals and letters (see Tables 1.5-6). In categories (C), seven divisions were composed to describe vaginal, urinary tract, rectal or bowel, skin and/or musculoskeletal and patients' specific complications. Each category is subdivided into further classes depending on category' criteria and description. The second component of the classification is time (T), which describes the time of clinical diagnosis of that complication. It has four divisions; the earliest time might involve insertion issues of the mesh/tape, whilst later divisions are usually related to healing abnormality issues. The third component of this classification describes the site (S) of the complication. As one might expect, possible sites of tape complications are vaginal, trocar passage, musculoskeletal, and intra-abdominal. One division is entitled as systemic complications with no specific site.

This classification was hoped to be useful for all parties involved in female pelvic floor surgeries like anti incontinence procedures and prolapse repair, including surgeons, physicians, nurses, and industry, so all of them will be referring to the same clinical issue in consistency. Examples of how this classification can be applied clinically are illustrated in Table 1.7.

IUGA/ICS classification has been evaluated and applied in study conducted by Petri et al. and results were published in 2012 (13). They studied 376 women with complications of synthetic slings, which were managed surgically, and after analysis of data, they found that new IUGA-ICS classification could be applied to most of the types of complications. However, de novo development of overactive bladder (OAB) was not included. The study recommended application of this classification in clinical practice with minor modifications such as inclusion of OAB as a complication of the synthetic sling surgeries. This recommendation was based on their review of complication cases in which they found that development of de novo OAB symptoms was the commonest complication encountered (13). However, still this classification is not widely adopted by neither clinical studies nor surgeons involved in management of SUI and/ or pelvic organ prolapse (POP) repair.

Table 1.5 International Urogynecological Association (IUGA)/International Continence Society (ICS) Joint Classification of Complications Related Directly to the Insertion of Meshes in Female Pelvic Floor Surgery: CATEGORY (C)

	General Description	A (Asymptomatic)	B (Symptomatic)	C (Infection)	D (Abscess)
1	**Vaginal** No epithelial separation	**1A** Abnormal graft finding on examination	**1B** Symptomatic (e.g. pain, dyspareunia)	**1C** Infection	**1D** Abscess
2	**Vaginal** Exposure >= 1cm	**2A** Asymptomatic	**2B** Symptomatic	**2C** Infection	**2D** Abscess
3	**Vaginal** Exposure < 2cm	**3A** Asymptomatic	**3B** Symptomatic	**3C** Infection	**3D** Abscess

	General Description	A (Asymptomatic)	B (Symptomatic)	C (Infection)	D (Abscess)
4	**Urinary Tract** Perforation, fistula, calculus	**4A** Small intraoperative defect (bladder perforation)	**4B** Other LUT Complication/ Retention	**4C** Ureteric or upper urinary tract complication	
5	**Rectal or Bowel** Perforation, fistula	**5A** Small intraoperative defect	**5B** Rectal injury or compromise	**5C** Small or large bowel injury or compromise	**5D** Abscess
6	**Skin and/ or Musculoskeletal** discharge, pain, sinus tract formation	**6A** Asymptomatic, abnormal finding on examination	**6B** Symptomatic e.g. discharge, pain or lump	**6C** Infection e.g. sinus tract formation	**6D** Abscess
7	**Patient** Compromise like hematoma	**7A** Bleeding complication	**7B** Major degree of resuscitation or intensive care	**7C** Mortality	

Table 1.6 An International Urogynecological Association (IUGA)/International Continence Society (ICS) Joint Classification of Complications Related Directly to the Insertion of Meshes in Female Pelvic Floor Surgery: TIME (T) and SITE (S)

TIME			
TI Intraoperative - 48 hours	**T2** 48 hours- 2 months	**T3** 2 months- 12 months	**T4** Over 12 month

SITE				
S1 Vaginal; **area of suture line**	**S2** Vaginal; away from area of suture line	**S3** Trocar passage Except S5	**S4** Other skin or musculoskeletal site	**S5** Intra-abdominal

Table 1.7 Examples of Complications Related to Mesh-based Surgery in Female Using the International Urogynecological Association (IUGA)/ International Continence Society (ICS) Joint Classification System

Patient ID	Clinical Description of Complication	Code	Code
100	Retropubic hematoma following a tape procedure (first 24 hours)	7A/T1/S3	
101	Persistent thigh pain six weeks after an obturator tape	6B/T2/S4	
102	Bowel obstruction and 2 cm vaginal vault exposure with bleeding six months after a mesh sacrocolpopexy	5C/T3/S5	3B/T3/S1

1.3.2 **Complications of Synthetic Slings Placed via Transobturator Approach**

The anatomic differences between the inside-out and outside-in approaches of transobturator tape (TOT) insertion have been compared, especially in terms of adverse outcomes. One method of studying such differences in anatomy was through cadaveric dissection of the pelvis after performing

sling surgery. When studying the inside-out technique of TOT insertion of the sling, the sling was found outside the pelvic space and did not penetrate the levator ani muscular group (2) (14). Risk of perforating bladder has been identified in those studies (2). Such injury is usually easily identified intraoperative if cystoscopy is carried out after passage of needle and tape.

Vaginal erosion and extrusion risk appears to be significantly related to mechanical properties of the mesh utilized. An incidence of up to 15% of vaginal extrusion and erosion had been reported with old meshes, and obturator and ischiorectal abscesses, sinus formation, and voiding difficulty were all noted (2). Newer polypropylene slings have lower incidence of erosion and extrusion.

Infectious complications also have been reported with TOT, such as abscesses, adductor myositis, and cellulitis (2). Cases of infected obturator hematoma requiring exploration and drainage have been also reported. As with vaginal erosion, risk of infectious complications decreased with the new slings. Urinary tract infection (UTI) has been reported to occur post TOT procedure in a rate between 7.4% and 13% (14), and it was under reported as postoperative complications, perhaps due to an improper definition and under reporting of UTI as a complication (14). It is usually managed with antibiotics with the same guidance and rules that govern the use of antibiotic for UTIsin other clinical scenarios.

Postoperative voiding dysfunction has an incidence between 2.1% and 6.7% after TOT techniques (2). Urinary obstructive symptoms rate varies between 1.5% and 15.6% of cases (2). They are usually temporary and managed with

short-term intermittent catheterization. Rarely, obstruction lasts longer than expected, and patients improve when the sling is incised or removed with a second operation (2).

Postoperative leg pain is a unique complication to TOT procedures, reported in up to 15.9% of patients (2) (14). It's usually transient, responds to non-steroidal anti-inflammatory medications, and improves shortly after surgery. It's likely due to subclinical hematoma or a transient neuropathic phenomenon (2). Pain can be felt down the leg or in the groin area. Cases that do not respond to conservative therapy should prompt investigation to role out tape erosion. Therapy with corticosteroids and local anesthetic agents might be required in some cases (2). Sling resection or urethrolysis sometime is needed.

1.3.3 Complications of Synthetic Slings Placed via Retropubic Approaches

Vaginal erosion or exposure of sling into vagina is a complication following TVT procedure, similar to TOT slings (2). It's manifested clinically by vaginal discharge, sexual discomfort or dyspareunia, non-specific lower urinary tract symptoms, and pelvic pain. However, up to one third of patients with vaginal erosion may be asymptomatic (14). Cases usually present within the first few weeks to few months of the procedure, and continence is usually maintained. Factors such as biomechanical properties of the mesh used, tissue healing and infection, thin, atrophic vaginal wall (as in post-

menopausal status), and incorrect surgical technique all were addressed as influencing factors to vaginal erosion (14). Cases are managed on individual basis, and conservative management, surgical removal of the exposed mesh, and even more aggressive surgical intervention has been reported to be effective in managing mesh erosion or exposure (2) (14).

Urethral erosion is a complication that can be associated with severe morbidity (14) (15). It's rare after retropubic approaches of sling placement surgery, with an incidence of less than 0.3% (2) (14). Possible risk factors include compromised blood supply to the urethra (such as post radiation cases), excessive sling tension or twisting of the tape, and iatrogenic urethral injury intraoperative. Also, surgical technique may increase the risk of urethral erosion, as carrying out dissection too close to the urethra can cause urethral devascularization (2). Patients with urethral erosion present in most instances with voiding dysfunction symptoms like urgency and urge incontinence, urinary obstruction and/ or retention, and recurrent UTI. Also, persistent urinary incontinence is a potential symptom of erosion of the tape into the urethra (2). Intraoperative cystoscopy is highly recommended to identify iatrogenic injury to the urethra. It makes a significant difference in the patient outcome if an injury is addressed at the time of the procedure. There is no role for conservative management for urethral erosion, and cases that present later have to be treated with an endoscopic procedure or transvaginal urethrotomy and excision of the exposed tape (2). In cases with more urethral lumen or surface compromise, graft may have to be considered for repair.

Bladder perforation while passing the needle to place the sling in the vaginal wound has been reported with retropubic approach. Rates range between 0.7% and 24%, and it's mostly related to surgeon experience, as incidence was noted to decrease when experience with the procedure increased (14). As with urethral injury, bladder perforation can be identified and corrected intraoperatively if cystoscopy is performed. The trocar is repositioned and the sling is placed in the appropriate place, and an indwelling catheter is left for a few days post operative (2). If it's not addressed intraoperative, the patients may presents with irritative bladder symptoms such as urgency and frequency. Some cases may present with fistulas with need for more aggressive intervention (14).

Intravesical tape erosion may be a distressing later symptom of bladder perforation if it was missed intraoperative. It is less common to have true erosion through the seromuscular layer of bladder (2). Typical symptoms might be lower abdominal pain, intermittent gross hematuria, recurrent UTI, frequency, urgency, and urinary incontinence. As with urethral erosion, ther is no role for conservative management in cases with intravesical sling erosion, and removal of a portion of tape with reconstruction of the urinary tract is the standard therapeutic approach (2). Patients usually maintain their continence if only the intravesical portion of the sling is removed.

Voiding dysfunction is a well-documented complication after all sling surgeries (2) (16). It usually presents as varying degrees of urinary obstruction (2) (13) (14). Reported incidence varies in different studies with rate between 1.9% and 19.7% (2) (14), and it seems that rate increases with prolonged follow up period (13). UDS has been used in multiple studies to

address parameters like urine flow, filling time, voiding time, and maximum voiding pressure, and compare those parameters before and after sling surgeries, thus, anticipate cases with possible post sling surgery voiding dysfunction. However, no enough evidences correlate UDS parameters with surgical outcome (2). Yet, it's vital to identify factors that might negatively affect outcome and predispose to post operative urinary retention, like age, parity, and peak flow rate on UDS (16). Also, it was found that patients who have lower detrusor voiding pressure are more likely to have urinary retention postoperatively (16). Another factor that may increase the risk of voiding dysfunction after sling surgery is concomitant prolapse surgery (16). Finally, local tissue criteria like abnormal positioning of the sling at bladder neck level, scarring of the bladder neck, and presence of paravaginal defects have been noted in patients with urinary obstruction (13). Hypothesized mechanisms for urethral obstruction after sling surgery included hyperelevation of bladder neck and/ or an exaggerated kink in the urethra (16). Clinical picture includes different presentations; patient may complain of difficulty in initiation urine stream, straining while voiding, incomplete emptying or total urinary retention (2). A thorough history and physical examination are vital in the initial evaluation and before any surgical intervention is carried out. Cystoscopy helps in the diagnosis mainly through exclusion of other causes of urinary obstruction. First line of management includes temporarily indwelling catheter use, intermittent catheterization, or timed and double voiding (2) (14). If symptoms persist, surgical intervention is advised. It's recommended to wait at least four weeks before surgical intervention is considered (2) (13) (14). Release of sling with minimal vaginal dissection is usually sufficient with maintained continence through the support of urethra from the remaining portions of the sling (2).

Other complications of sling surgery have been reported in minor percentages. Wound–related complications like infection, abscesses and UTI have been addressed. Serious complications like vascular injury and hemorrhage into pelvis have been also reported, and at least one case leading to mortality (2) (14). Postoperative dyspareunia has been reported in up to 15% of patients who underwent sling surgery (2) (14). It was attributed to the physical properties of the sling that cause shrinkage and/ or migration.

Review of the safety database of U.S Food and Drug Administration for complications reported to that agency is listed in Table 1.8.

Table 1.8 Summary of All significant Complications Reported to the U.S Food and Drug Administration with Midurethral Sling (1998-2009)

Complication	No. Of cases reported
Bladder erosion	50
Urethral erosion	51
Vaginal erosion	239
Bowel perforation	48
Major vascular	26
Blood loss > 200ml	36
Plastic sheath malfunction	51
Leg pain	44
Needle broken from mesh	154

2 Literature Review

Complications of synthetic sling surgery can be related to patient's factors, provider' factors, surgical techniques, and the physical properties of sling itself. In the literature, complications were mainly described in relation to their time of diagnosis in postoperative follow up, or in relation to surgical approaches commenced in the surgery. As described previously, a recent classification system was standardized by IUGA and the ICS joint committee to describe and diagnose complications related to meshes, tapes, or implants surgery in female, however, it is not yet widely used in evaluation of those complications either in clinical practice or in literature.

2.1 Food and Drug Administration (FDA) Warning about the Use of Surgical Mesh for SUI

After the approval of synthetic sling use in United States (USA) in 1998 by the Food and Drug Administration (FDA), urologists and gynecologists all over the world started performing mid-urethral sling surgeries. In 2011, over 3 million mid-urethral slings had been sold worldwide (17). The procedure is considered safe, however, in October 2008, FDA issued a public health notification (and updated it on July 2011) about slings and meshes used in gynecological surgery (18) (19). The notification was issued after the agency received more than 1,000 reports of complications associated with the use of meshes for both pelvic organs prolapse (POP) repair and SUI correction.

Vaginal erosion, pain, infection, and recurrence of prolapse and/or incontinence were among those rare complications (18). FDA did not advise cessation of surgical meshes usage; it did recommend "specialized training for mesh placement technique" and thorough counseling with patients about properties of mesh, and "that complications associated with the implanted mesh may require additional surgery that may or may not correct the complications" (18). The updated statement issued in 2011 had a significant distinction: "serious complications associated with surgical mesh for transvaginal repair of POP are not rare", and it was plainly stated that POP repair with mesh is "not clearly more effective than traditional non-mesh repair". Indeed, mesh may expose patients to "greater risk" compared to traditional surgical approach (19). This severed to separate mesh used for POP compare to mesh used for SUI surgeries. However, the FDA did not declare special concern related to SUI surgeries using synthetic mesh, and most complications were related to POP surgeries using mesh. That being said, the FDA in 2013 stated explicitly "that safety and effectiveness of multi-incision slings is well established in clinical trials that followed patients for up to one-year" (20), and there were no recommendations or advice to chose non mesh-based intervention for SUI. None of the FDA communications or notifications regarding mesh use in pelvic reconstructive surgery in general was related to a recall (17).

It was necessary to discus the warnings and concerns of the FDA regarding surgical use of mesh in pelvic surgery due to the confusion that occurred in both parties involved in this issue: health practitioners and patients, especially with the appearance of different reports and investigations in media and the commencement of multiple lawsuits in U.S and Canada.

2.2 Complications Rates in Literature

A literature search for the incidence of complications associated with synthetic sling use in SUI can be quit difficult. Investigators tend to report complications of synthetic slings that were placed during POP repair procedure, which can makes such results confusing. Another challenging issue is the ambiguous terminology of different complications used in different studies and reviews. For example, voiding dysfunction can be defined as the inability to void completely, inability to empty the bladder comfortably, or dysuria, which is confusing, and many articles do not specify the definition they use. Likewise, pain may be reported post operatively as complication; most articles didn't use a pain scale either initially or in follow up.

Characteristics of patients reviewed are another limitation when assessing incidence rate of sling-related complications, as most of the patients were not homogenous in their surgical history, and several studies did not differentiate between patients who underwent sling surgery as primary anti-incontinent surgery and those who had recurrent SUI treated with previous sling or non-sling procedure. All those factors may contaminate the true rate of complications of synthetic sling surgery as a variable, and influence the analysis of true factors likely causing those complications.

One last issue about the true incidence of complications is the actuality of reported complications in literatures. Many centers and health practitioners

in the world do not publish articles or studies about synthetic sling complications for different reasons; they would just report them to the local authorities according to established protocols in their administrative setting. This may present literature with an inaccurate complications rate, which was demonstrated in one study that compared complications rate reported in literature between 2001 and 2005 with the rate found in FDA's Manufacturer and User Device Experience (MAUDE) database (21). There was significant discrepancy between the two rates with the one reported in MAUDE higher than those published in literature. The authors explained this difference with the fact that some complications related to urethral and bladder perforation can present with mild urinary symptoms, which make them less likely to be reported (21).

2.3 Perioperative and Immediate Postoperative Complications

As mentioned previously, synthetic sling- related complications could be categorized in relation to their clinical presentation timing to perioperative or immediate postoperative complications, and late postoperative complications. We'll discus here incidence rate of perioperative and immediate postoperative complications.

2.3.1 Bladder Perforation

A meta-analysis of randomized controlled trials that compared tension-free midurethral tapes to other surgical procedures carried out by Novara et al in

2008 showed that retropubic approaches was more likely to cause bladder perforation (22). This was evident in other studies (14) (23), and several systematic reviews (24) (25) (26). Novara et al did update their systematic review two years later and found the same result regarding bladder perforation risk (27). Stanford et al found in their review of all urethral slings complications that overall incidence of abdominal and pelvic organ injury including bladder was 3.3% (28), however, intraoperative bladder perforation rates of up to 24% have been reported (29).
Incidence of bladder perforation/injury in retropubic approaches in general is low, as reported by Kuuva et al in their nationwide analysis of TVT sling procedure and Abouassaly et al in a multi-institutional review as 3.8% and 5.8%, respectively (30) (31).

2.3.2 Urethral Injury

The urethra is also at risk of injury during SUI corrective surgery using a synthetic sling. One review of urethral injury rate showed no statistically significant difference in its incidence between retropubic and transobturator approaches (29). However, a meta-analysis done by Schimpf et al. showed that urethral injury cases were fewer in the transobturator approach (25). Authors in the former review reported a median incidence rate of urethral injury at both retropubic and transobturator approaches to be 0.88% (range 0.1-5.5%) and 1.09% (range 0.0-2.5%), respectively. They identified risk factors like previous pelvic surgery, infection, radiotherapy, and experience of the surgeon. Along with their literature review, authors also reported 14 cases of urethral injury identified in their center, and they concluded based on their criteria and findings that fistula, diverticulum formation and

symptomatic outflow obstruction are serious squeals to urethral injury, and recurrent or persistent stress urinary incontinence is common, for which they recommended cystourethroscopy as part of all mid-urethral sling procedures.

2.3.3 Major Vascular Injury

Major vascular injury during synthetic sling surgery can be serious, although rare in occurrence. Vascular injuries involving large arteries like the external iliac, femoral, obturator, epigastric and inferior vesical have been reported (14). A review of the FDA MAUDE database between 2001 and 2005 revealed 36 cases of major vascular injury including three deaths (21). Incidences between 0- 0.1% have been reported in four national registries of synthetic slings procedures (32). Kuuva et al in their evaluation of 1455 cases reported an incidence of 0.07% for major vascular injury (30).

In a study to avoid vascular injury, Muir et al reviewed and described the vascular anatomy of lower pelvis in relation to insertion of tension-free vaginal tape (33). They used fresh frozen cadavers in their study, and they performed tension-free tape insertion in three different planes in relation to needle passage, then they evaluated distance to different vessels. The mean distance from the tape needle to the obturator vessels was the closest: 3.2 cm (range 1.6–4.3 cm). The mean distance from the tape needle to the superficial epigastric vessels was 3.9 cm (range 0.9–6.7); to the inferior epigastric vessels, 3.9 cm (range 1.9–6.6 cm); and to the external iliac vessels, 4.9 cm (range 2.9–6.2 cm). When the needle was directed 6 cm lateral to the mid–biceps brachii muscle (according to planes already constructed), the external iliac vein was punctured.

2.3.4 Voiding Dysfunction

Voiding dysfunction is a common complication after synthetic sling surgery, and symptoms can be related to storage phase or voiding phase. Reviewing the literature for voiding difficulty is challenging because of its inconsistent definition among different studies. Some studies and reviews differentiate between incomplete emptying (as manifested by post void residual more than 100 ml) and complete retention. Other studies don't do that and only report, "voiding dysfunction" without clear definition. This makes evaluation of its true incidence a very difficult target. Added to this, the heterogeneity of patients reviewed in their past surgical history makes it doubtful to attribute postoperative voiding difficulty to the sling procedure solely.

The incidence of voiding lower urinary tract symptoms (LUTS) varies between 3.3% up to 54.9% in randomized controlled trials assessing different surgical kits in the retropubic approach (22). In an analysis of 404 cases of SUI who underwent tension-free vaginal tape procedure in prospective multicenter study, voiding difficulty was noticed in 4% of patients (34). Abouassaly et al noticed in their multi-institutional review that 19.7% of patients who underwent tension-free tape had a urinary retention for more than 24 hours postoperative (31), almost two-thirds of them were in retention for less than 48 hours, and the other one-third were treated with an indwelling catheter or clean intermittent catheterization for a mean period of 22 days. In seven patients the tape was released to treat the retention, and it was sectioned in three. Kuuva et al reported low incidence rates of both

minor voiding difficulty and complete urinary retention as 7.6% and 2.3%, respectively with retropubic approaches of sling placement (30). Difficulty in emptying and/or retention were the main presenting symptoms in 9 out of 21 cases of retropubic sling procedure at a tertiary referral center (21). Cases varied in their presentation time; 6 cases presented immediately postoperatively, and the other 3 presented in less than two weeks.

Several comparison studies and meta-analysis found no statistical/clinical significance in immediate postoperative voiding difficulty between retropubic and transobturator approaches of synthetic sling placement (24) (25) (27) (35) (36). Reported rates of postoperative obstruction after synthetic slings surgery in general range from 1.9% to 19.7% (14). In one review by Petri et al, however, obstruction was noted in 48% of patients presented with complications (13). Interestingly, analysis of 233 cases underwent TOT sling procedure with 27 months follow-up found no difference in term of urinary retention earlier in postoperative period between women who had sling surgery compared to women who had sling surgery and another surgical procedure (37).

2.3.5 Other Complications

Other immediate postoperative complications like UTI, groin pain, hematoma and wound related complications were also reported in the literature. Table 2.1 summarizes some of those complications reported in selected articles.

Table 2.1 Non-frequent Reported Complications Related to Synthetic Slings in Different Studies

Reference	No. Of Case	Follow-up (Months)	Hematoma (%)	Groin/ Thigh pain (%)	Wound related	UTI (%)
Kaelin-Gambirasio et al (37)	233 (TOT)	27	0.4	NR	NR	NR
Petri et al (13)	359 (Suburethral Slings)	> 120	2	2.5	1.6	10
Abouassaly et al (31)	241 (TVT)	NR	1.9	NR	0.4	12
Meschia et al (34)	404 (TVT)	35	1.5	NR	0.5	NR
Neuman M (38)	300 (TVT-O)	4-24	NR	NR	NR	0
Karram M (39)	350 (TVT)	48	1.7	NR	0.9	10.9

2.4 Late Postoperative Complications

Long-term follow-up of patients who underwent synthetic sling surgery for SUI may help to detect late postoperative complications as soon as they are evident, so proper medical intervention can be initiated immediately. Two complications commonly reported in long-term follow-up after synthetic sling surgeries are discussed here.

2.4.1 De novo Urgency and Urge Incontinence

De novo urgency was among the commonest long-term complications reported after synthetic sling surgery for SUI. It was noted with other irritative LUTS after synthetic sling surgery. It's incidence varied between 0 to 25.9% in different studies(14). Recent meta-analysis showed that postoperative overactive bladder (OAB) symptoms were more common in patients who had retropubic slings (25). Novara et al reported similar findings in their updated systematic review, although when they did meta-analysis of high-quality RCTs no statistical significance was noted (27). Urgency and/or urge incontinence can be an early sign of mesh misplacement, whether in urethra, bladder neck, or bladder itself. Deng et al in their review of complicated cases post synthetic slings procedures found mesh in the urethra and/or bladder in ten cases presented with irritative LUTS (21). Holmgren et al did another review that included 463 women who had TVT for genuine SUI for de novo urgency incidence and found it to be 14.5% (40). Based on their analysis of all women criteria, they found that older age, parity, and history of cesarean section were significant risk

factors. Petri in his review of 359 cases of synthetic sling surgery complications concluded that de novo OAB seems to be the commonest complication with rate of 54% (13). He did recommend changes in the new IUGA-ICS classifications of complications to adapt this complication.

2.4.2 Vaginal Erosion

Vaginal erosion is defined as "the presence of foreign material (sutures, sling material) within the vagina after vaginal wound healing" (41). It used to be reported more commonly, which could be attributed to the types of meshes used initially and their mechanical properties. Also, types of surgical devices that were available in the market previously contributed to higher rates of erosion, for which they were recalled because of their overall higher risk of complications (14) (27) (37). Lack of cumulative experience with both proper wound dissection and proper placement of tape are other influencing factors.

A prospective study by Chen et al analyzed the possible risk factors for vaginal tape erosion after synthetic sling surgery in 233 women who underwent sling surgery for SUI (41). They reported erosion in 6 patients, and among clinical risk factors they assessed for erosion only diabetes mellitus (DM) was a significant one. Thus, they advised counseling women with DM that vaginal erosion is a possible complication after tape procedure. Another analysis of 233 women who underwent TOT procedure found that age, body mass index (BMI), and concomitant pelvic procedure were not statistically significant risk factors for erosion (37). Petri et al in their review of 359 cases with synthetic sling related complications reported

vaginal exposure in 68 patients (13), and it was among the commonest three complications in that group.

Two meta-analysis reviews compared the retropubic to the transobturator approach in vaginal erosion risk, and found increased risk with the transobturator approach (24) (25). On the other hand, another meta-analysis done in 2008 and updated in 2010 found no statistically significant difference between the two approaches (22) (27). Tommaselli et al did a recent meta-analysis, and found that transobturator approach in synthetic sling surgery was associated with increase risk of both vaginal injury and erosion (26). This discrepancy could be explained by the criteria of the RCTs included in those meta-analyses. Another possible reason is the inclusion of studies reported on use of older surgical device for transobturator insertion of synthetic sling, which was known to be associated with a higher incidence of erosion.

3 Methodology

The purpose of our study was to: 1) estimate the incidence of synthetic sling removal after synthetic sling surgery for SUI, 2) assess the possible impact of surgical volume and specialty of the provider surgeon on this incidence, and, 3) to evaluate other risk factors for sling removal.

3.1 Study Design

We conducted a retrospective population-based cohort study examining all adult women who underwent a SUI synthetic sling procedure in the period between April 2002 and December 2012 (fiscal year 2002/03 to 2011/12). Our study was conducted in Ontario, Canada, a province of over 13 million residents (42) with nearly universal health care access, and coverage of government funded health care system. No patient consent was required as our data were administrative in nature. The research ethics board at Sunnybrook Hospital, Toronto, Canada, approved the study.

3.2 Data Source

Data regarding the cohort, outcome, and different variables measured were collected using linked health care databases via Institute for Clinical Evaluative Sciences (ICES), which is a not-for-profit research institute made up of a community of research, data and clinical experts, and a secure and

accessible set of Ontario's health-related data such as population- based health surveys, as well as clinical and administrative database (43).

Canadian Institute for Health Information (CIHI) was one source of data in our study. It manages a number of databases as part of its contribution to the health care system in Canada. Discharge Abstract Database (DAD) and Same Day Surgery (SDS) are two of those databases, and were used to identify our cohort with their primary and secondary diagnosis, day- surgery procedures, discharges, and death records.

The Ontario Health Insurance Plan (OHIP) database was also used in our study. The ministry of health maintains it and it has records for all physicians' payments to Ontario doctors. It also includes all claims submitted whether services were on an inpatient or out patient basis.

Data quality measures have been carried out to ensure a high-quality administrative data in all three data sources. One measure was through conducting a review of published and unpublished studies in Canada to assess the completeness of data and the level of agreement across different databases (44) (45). Quality of data was assessed through three criteria: Completeness of the data, agreement of information when data from one database was compared to the same information obtained from another database, and agreement of diagnosis with experts' opinion. After this review that was done in 2000, it was concluded that demographic information on patient age, sex and residence was complete and reliable, and there were a high levels of agreement on specific surgical procedure codes

found in hospital discharge data and medical claims (45). Also, billing claims for physician services provided complete capture of procedure codes.

3.3 Patients Population

All adult women above the age of 18 years who underwent SUI synthetic sling procedure in Ontario in the period of April 2002 to December 2012 were identified and included in our study. Canadian Classification of Health Intervention (CCI) codes from the CIHI-DAD/SDS database were used to identify the patients (Appendix B). CCI code system is the standard coding system used for classification of health-related interventions in Canada, and it is the companion classification system to International Classification of Disease (ICD) in its 10^{th} revision (46).

The CCI coding system was revised more than once through adding new codes and updating existing ones to accommodate new procedures and surgical approaches. These changes were considered in identifying cohort patients in our study. Also, as different surgical kits had different entry times to the markets, possible CCI codes for all different kits were assessed, revised and included during data collection.

We set a look back window of five years prior to index date to prevent contamination of our primary outcome and to ensure completeness and validity of the data. Certain exclusion criteria (Table 3.1) were applied to cohort patients using OHIP and CCI codes for the same above reasons. Prior

pelvic surgical interventions using meshes like anti incontinence surgery or POP repair can influence the result of index synthetic sling surgery, thus affect its complications whether in nature of complication or its prevalence. So, such cases were excluded. However, patients who underwent simultaneous or subsequent non-mesh based POP surgery were included in the study to monitor the effect of concomitant pelvic surgery on SUI surgery.

Table 3.1 Exclusion Criteria in Cohort Patients

Exclusion Criteria
Prior incontinence surgery
Prior vaginal prolapse repair surgery
Additional SUI/POP surgery performed within 1 week of index event
Neurogenic diagnosis

As patients were identified through linked administrative databases, additional exclusion criteria were applied for data cleaning to ensure the highest quality of data. For examples, patients with missing or invalid health record number, missing or male sex, and missing birth date were excluded. In addition, patients who were not permanent residents in Ontario were excluded to ensure best longitudinal follow up for cohort.

All these exclusion criteria were assessed and applied using CCI/CCP and OHIP codes as mentioned previously. Such codes could be traced back to 1992, when a well-established electronic coding system using CCI was available and traceable.

Index date was assigned as the date of SUI surgery using synthetic mesh, and observation of cohort was continued until death, first occurrence of an outcome, date of last contact of patient with health care system as follow up plus one year, or the end of the study, that was determined by March 31st 2013.

3.4 Primary Outcome

The primary outcome was defined as the first reoperation for SUI mesh-related complications. CCI codes were used in identifying outcome, and all possible codes related to mesh complications surgeries were included. For example, codes related to removal of foreign body in urethra, division, extraction of foreign body in vagina, and urethrolysis were included. Also, codes describing endoscopic treatment of foreign body or mesh encrustation in bladder were assessed and included. In an attempt to include all operations related to SUI mesh sling complications in the cohort, CCI codes specific to management of bladder neck slings were included, like removal of internal device (i.e. sling), taking into considerations different approaches (like open, vagina, endoscopic). Different CCI codes used to define primary outcome are outlined in Appendix C.

When two outcomes were found in one patient, the first recorded one was marked as the primary outcome. Any CCI code with less than 6 in number of patients (i.e. number of patients experienced outcome with that CCI code) its actual value was not reported for privacy issues.

3.5 Primary Exposures

Surgeon volume and surgeon specialty were identified as primary exposures of interest in our study. Surgeon volume was defined as the number of synthetic sling procedures for SUI done per year, which is assessed by the hospital administration on a yearly basis. Surgeons are categorized in databases as high-volume and low-volume providers. High-volume surgeons are defined as being above or at the 75^{th} percentile for sling surgery number in a given year, and surgeons' status could change from high to low-volume category and vice versa; surgical volume was checked on a yearly basis. This was considered and included in our study data, and it was tracked via CIHI-DAD/SDS databases.

Surgeon specialty was determined as urologist, obstetrician/gynecologist, or undetermined. It was also accessed via CIHI-DAD/SDS database. Undetermined group of surgeons who did the synthetic sling surgery were created after failure to specify their specialty through database.

3.6 Secondary Exposures

As our study was designed to be both a descriptive and analytic observational cohort with a large number of patients, we also evaluated the effect of other factors on the incidence of reoperation for SUI sling-complications. The number of implanted slings to treat SUI was evaluated as one of the secondary exposures. So, we identified all patients who had two

or more synthetic mesh implant to treat SUI and we assessed their risk for higher incidence of complication- related surgery.

Patients with known risk factors for synthetic sling complications were evaluated as one group. Those factors are: previous urinary fistula, urethral diverticulum, pelvic radiation and urethral injury. Diagnosis of these conditions was identified by CCI codes in the cohort patients. They were examined as a secondary exposure.

The setting of health facility that sling was implanted in was evaluated as possible risk factor for sling complications occurrence. Hospitals were categorized as academic and community hospitals, and patients' initial sling implant was grouped accordingly.

Other risk factors that might affect the incidence rate of reoperation after SUI sling surgery included: age, concomitant pelvic surgeries at the time of sling implant without mesh (like POP repair), obesity, and DM. They were considered as secondary exposures and evaluated independently.

All those covariates were defined using different defining codes from both databases of OHIP and CIHI-DAD/SDS (Appendix D). A summary of both primary and secondary exposures evaluated in our study is obtained in Table 3.2.

Table 3.2 Primary and Secondary Exposures

Primary Exposures
Surgeon Surgical Volume
Surgeon' Specialty
Secondary Exposures
Age
Concomitant surgeries (Hysterectomy, POP repair)
DM
Obesity
High risk patients (H/O urethral diverticulum, urethral injury, urinary fistula, pelvic radiation
Multiple synthetic sling implant for SUI
Academic hospitals

3.7. Statistical Analysis

As mentioned previously, one of our objectives was to evaluate specific factors (as an independent variables) on the rate of reoperation for SUI complications. An important variable was surgeon' surgical volume, so, we subcategorized patients into two groups and reported baseline characteristics based on high and low volume surgeons. Baseline characteristics are reported in Table 3.3. Those criteria were reported in either numbers with corresponding percentage or medians with their corresponding interquartile range (IQR). IQR was used as out measure of spread of our data points.

Table 3.3 Reported Baseline Characteristics of Patients

Characteristics of Cohort Patients
Age
Obesity (BMI > 40)
DM
Concomitant hysterectomy
Prior hysterectomy
Prior non-mesh-based surgery for POP
Concomitant non-mesh-based surgery for POP
> 1 Synthetic sling implant for SUI
High risk patients
Fiscal year of cohort entry (Index date)
Surgeon specialty (Urology, Obstetrics/gynecology/unknown)
Teaching hospitals
No. Of health care resources used 1 year before synthetic sling implant for SUI
Death after index date
Emigration

Comparability of the two groups of cohort patients on their baseline criteria was carried out using standardized differences of the mean (SDM), which is more informative than traditional hypothesis testing, especially in large sample/group size of observational research as our study had (47). To measure strength of any association between surgical volume and different enlisted baseline criteria, a standardized difference of more than 10% (or 0.1) was considered significant (48).

We conducted a multivariable survival analysis as primary analysis for our data, and we included surgeon' volume, surgeon' specialty, high-risk patients, and the multiple mesh implanted group. Our study examined the

cohort patients with different index dates over ten years (i.e. different entry points) and different time period to complication surgery (primary outcome). For which, hazard ratio (HR) with confidence interval (CI) was calculated to estimate the risk of primary outcome over the study time period. CI of 95% was reported for clinical significance.

Multivariable analysis was run using the PROC PHREG procedure in SAS software (version9.3; SAS Institute Inc.), and a Cox proportional hazards regression model was used to assess the effect of different covariates on the outcome over time. We adjusted for age, obesity, diabetes, concomitant hysterectomy, prior hysterectomy and/or non-mesh-based surgery for POP, concomitant non-mesh-based surgery for POP and hospital type. Cumulative incidence rate of outcome was calculated using Kaplan- Meier survival analyses, and Cochrane –Armitage test was used to assess the linear trend of outcome and significant changes in the 1-year event rate over time.

4 RESULTS

4.1 Baseline Characteristics

We identified 61,876 women who underwent synthetic sling implant for SUI (Figure 4.1). 1,989 patients were excluded according to our predefined exclusion criteria listed in table 4.1. A final cohort of 59,887 patients was reviewed and analyzed, out of whom 1,740 patients died and 915 patients were lost to follow up (identified by date of last contact with health care system plus 1 year). We reached the end of the study with 55,925 patients. The number of patients enrolled per fiscal year is outlined in figure 4.2 (as our study endpoint was predetermined to be December 31st 2012, and fiscal year starts on April 1st and ends on March 31st, the rest of data for 2012 were extrapolated from the period January 2013-March 2013 based on available data of the first 9 months), and a steady increase in patients' number is observed, likely due to the increase in popularity of synthetic slings as minimally invasive procedure to treat SUI. Another possible reason is the practice of "prophylactic MUS surgery" when performing POP repair.

Median age of patients was 52 years (IQR, 45-63), and median follow-up was 4.4 years (IQR, 2.3-6.8). Surgical procedures were done by total of 1,068 surgeons, out of whom 625 were gynecologists (58.5%), 293 were urologists (27.4%), and 150 (14%) were undetermined. Patients were categorized according to surgical volume of their operating surgeon into two groups (Table 4.2). High-volume surgeons were defined by being at the 75th percentile or above for procedures performed for SUI yearly. They operated on 44,140 (73.7%) patients (Figure 4.3).

Table 4.1 Cohort Patients' Exclusion Criteria

Exclusion Criteria	No. Of patients
Age < 18 years or > 100 years	9
Male/Missing gender	507
Non Ontario residence	37
Use of vaginal mesh for prolapse prior to 1st of April 2002	594
Use of vaginal mesh for prolapse after 1st of April 2002	507
Prior use of mesh for SUI	56
Missing hospital institution	279
	Total = 1989

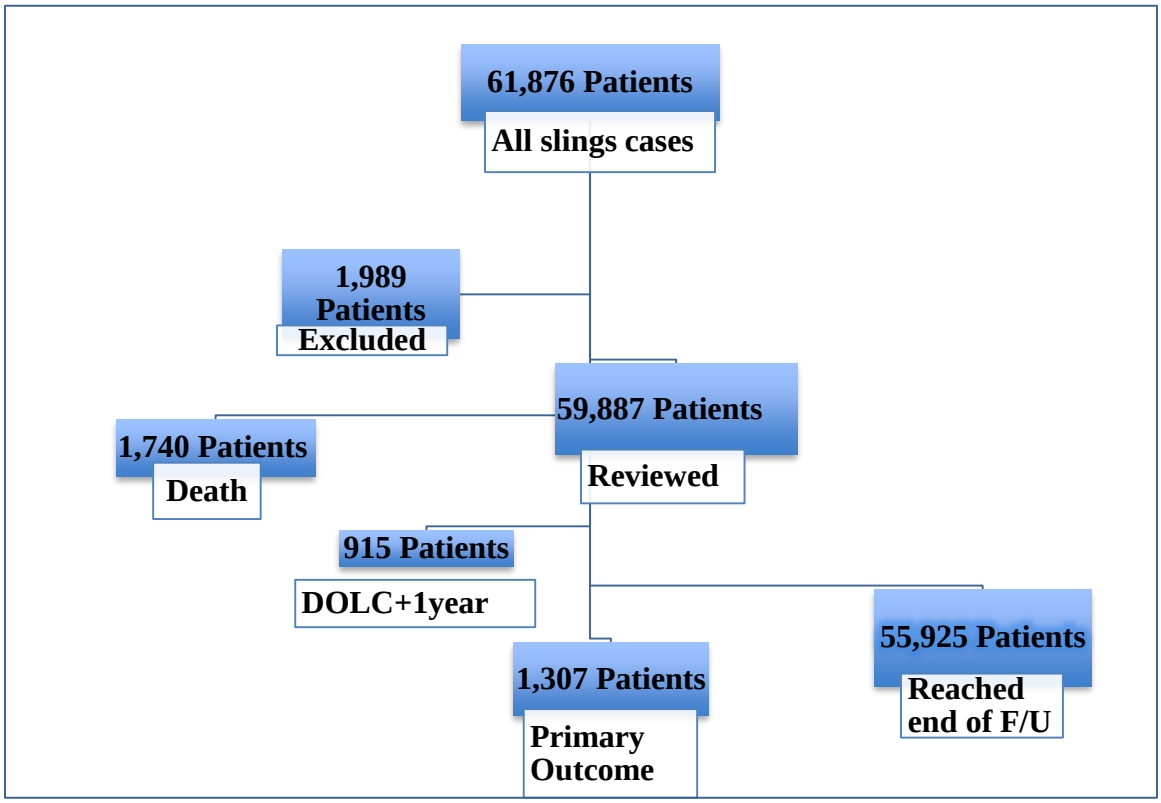

Figure 4.1 Flow Chart of Cohort Patients

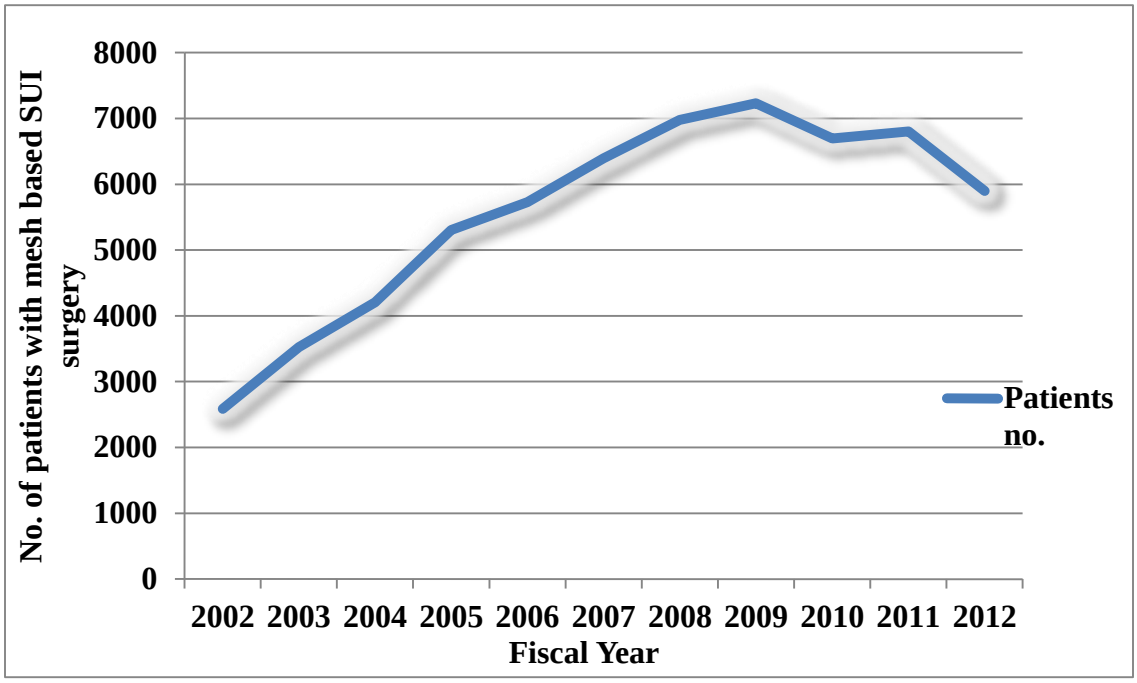

Figure 4.2 Number of Patients Who had Mesh-based SUI Surgery Per Year between 2002- 2012. Note that number of patients in 2012 was derived from combined data from both fiscal years 2012 and 2013 (see text)

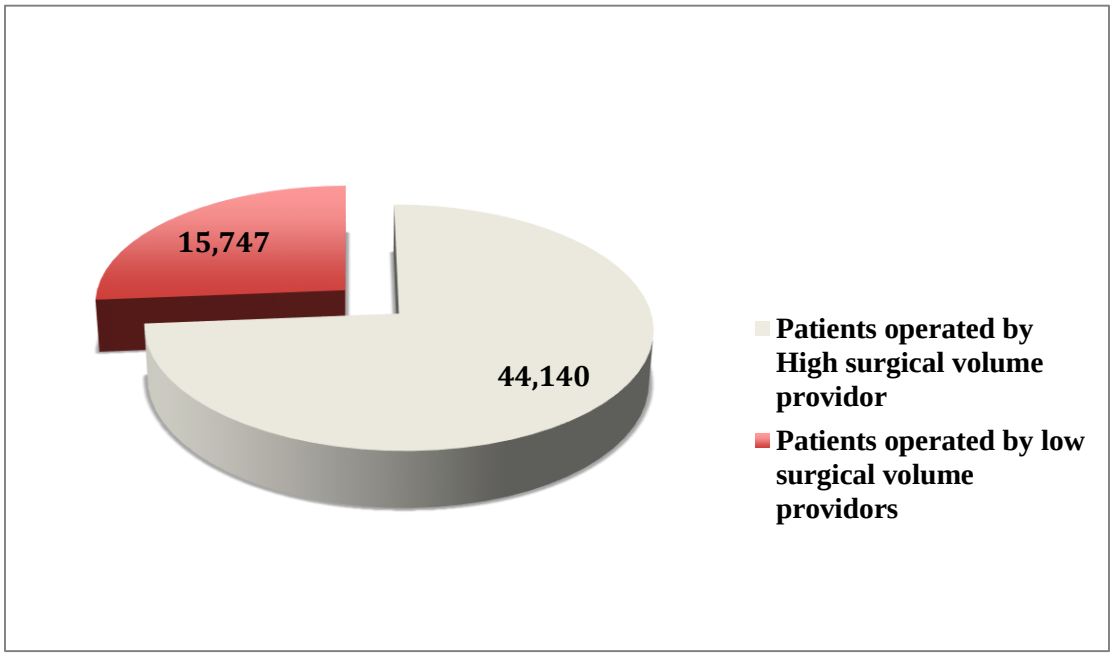

Figure 4.3 Cohort Patient's Distribution According to their providers' surgical volume.

Table 4.2 Baseline Criteria of Patients in Relation to Surgeon' Volume

	High -Volume Surgeons [a] **(n=44140)**	**Low-Volume Surgeon (n=15747)**	**Standardized Difference of the Mean**[b]
Age, median (IQR), years	53 (45-63)	52 (45-63)	0.02
BMI >40, number (mean)	1976 (4.5)	698 (4.4)	0
Diabetes mellitus, number (mean)	5222 (11.8)	2036 (12.9)	0.03
Concomitant Hysterectomy, number (mean)	5061 (11.5)	2603 (16.5)	0.14
Prior Hysterectomy, number (mean)	3633 (8.2)	1329 (8.4)	0.01
Concomitant non-mesh-based surgery for POP, number (mean)	13115 (29.7)	4743 (30.1)	0.01
Prior non-mesh-based surgery for POP, number (mean)	2386 (5.4)	805 (5.1)	0.01
> 1 Synthetic sling implant for SUI, number (mean)	900 (2.0)	352 (2.2)	0.01
High risk patients [c], number (mean)	54 (0.1)	19 (0.1)	0
Fiscal year of cohort entry (index date), number (mean)			
2002	1917 (4.3)	668 (4.2)	0
2003	2664 (6.0)	859 (5.5)	0.02
2004	3199 (7.2)	1005 (6.4)	0.03
2005	4056 (9.2)	1251 (7.9)	0.05
2006	4144 (9.4)	1584 (10.1)	0.02
2007	4727 (10.7)	1669 (10.6)	0
2008	5218 (11.8)	1759 (11.2)	0.02
2009	5177 (11.7)	2055 (13.1)	0.04
2010	4836 (11.0)	1859 (11.8)	0.03
2011	4969 (11.3)	1835 (11.7)	0.01
2012	3233 (7.3)	1203 (7.6)	0.01

	High -Volume Surgeons [a] (n=44140)	Low-Volume Surgeon (n=15747)	Standardized Difference of the Mean[b]
Surgeon specialty			
Urology number (mean)	18946 (42.9)	6648 (42.2)	0.01
Obstetrics/gynecology	25133 (56.9)	8837 (56.1)	0.02
Unknown number (mean)	61 (0.1)	262 (1.7)	0.17
Teaching/academic hospital	12762 (28.9)	2562 (16.3)	0.30
No. Of health care resources used 1 year before synthetic sling implant for SUI number (IQR)			
Family Physician visits,	6 (3-9)	6 (3-9)	0.05
Urology or Gynecology Visits number (IQR)	2 (1-3)	3 (2-4)	0.26
Hospital admissions	0 (0-0)	0 (0-0)	0.04
Death after index event	1289 (2.9)	485 (3.1)	0.01
Emigration	683 (1.5)	232 (1.5)	0

Abbreviations: IQR, interquartile range; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); POP, pelvic organ prolapse.

a High volume surgeon is defined to be at or above the 75th percentile for mesh implants for SUI in a given year.

b A value of greater than 10% (0.1) is considered a meaningful difference between the two groups.

c Includes patients with fistula, urethral diverticulum, urethral injury, or post radiotherapy.

Significant differences between high and low-volume surgeons appear in their clinical practice. High-volume surgeons (urologists or gynecologists) saw patients less frequently before their SUI sling surgery (median, 2 [IQR, 1-3] vs. 3 [IQR, 2-4] visits; standardized difference, 0.26). They also were less likely to do concomitant hysterectomy with SUI surgery (11.5% vs.

16.5; standardized difference, 0.30), and they were more likely to do the procedure in academic hospitals (28.9% vs. 16.3%; standardized difference, 0.30).

4.2 Primary Analysis

A total of 1307 women (2.2%) had the outcome, (removal or revision of their mesh implant for SUI). Their distributions according to their provider' surgical volume and specialty is illustrated in figures 3 and 4. The median of time between original mesh-based procedure for SUI and removal date among the 1307 patients was 0.94 (IQR, 0.35-2.49) years (Table 4.3).

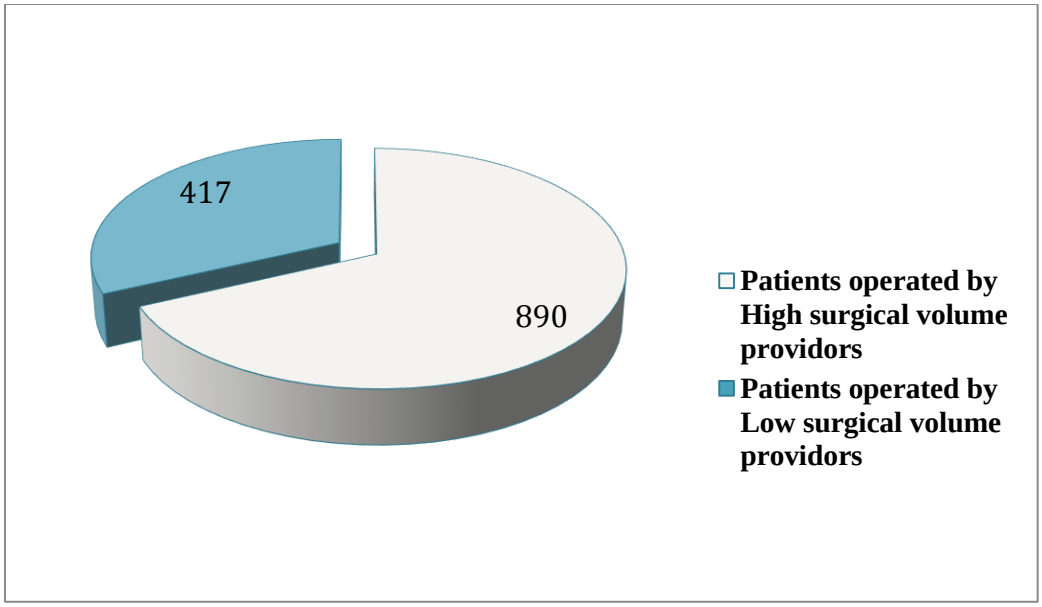

Figure 4.4 Description of Patients with Outcome in Relation to Their Provider' Surgical Volume

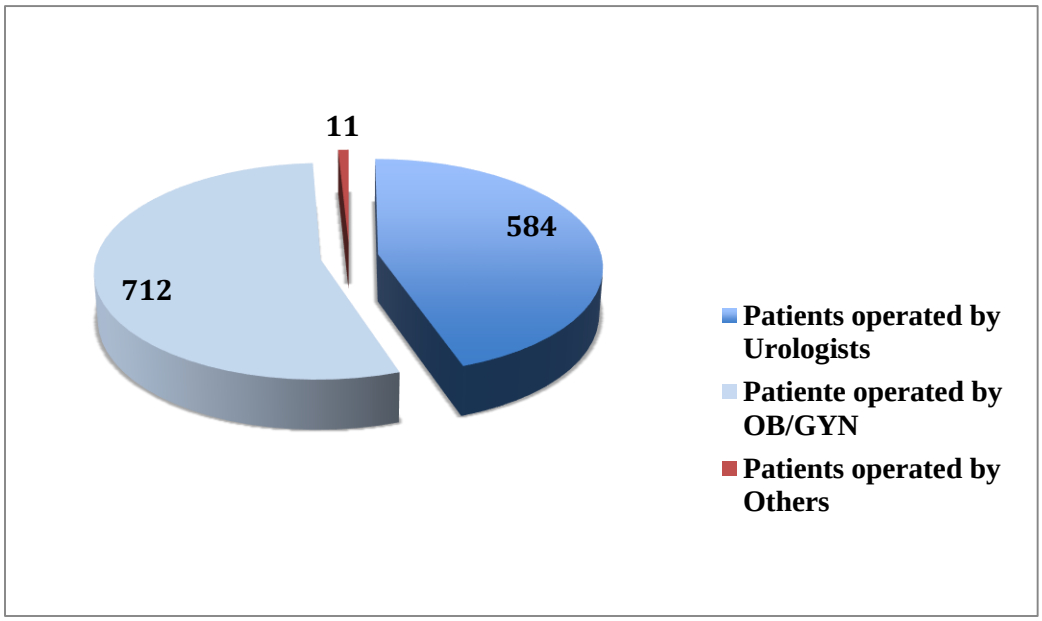

Figure 4.5 Description of Patients with Outcome in Relation to Their Provider' Specialty

Table 4.3. Mesh Revision/ Removal After Mesh-Based Surgery for SUI

	Entire Cohort (n=59,887)
Duration of follow-up, median, (IQR), years	4.43 (2.35-6.88)
Total follow-up, person-years	282,801
Outcome, No. of patients, %	1307 (2.2)
Time from index date to outcome, median (IQR), years	0.94 (0.35-2.49)
Event rate per 1000 patient-years of follow-up (95% CI)	4.62 (4.38-4.88)

Calculation of cumulative incidence rate of outcome showed steady increase over 10 years from 1.17 (95% CI, 1.09-1.27) at year 1 post index date to 3.29 (95% CI, 3.05-3.53) at 10 years post index date. Table 4.4 shows the cumulative incidence rate by years of follow up.

Unadjusted analyses of patients who underwent revision or removal of mesh showed that low-volume surgeons had a 37% ($p < 0.0001$) increase in relative risk for mesh removal or revision in their patients compared to high-volume surgeons (Table 4.5). However, there was no significant difference in rate of revision or removal of the mesh between gynecologists and urologists (RR, 0.92; 95%CI, 0.82-1.02). Table 4.6 shows the unadjusted analyses of patients who underwent mesh removal or revision in relation to their provider' specialty.

Table 4.4 The Cumulative Incidence Rate of Mesh Revision/ Removal After Mesh-Based SUI Surgery

Year	No. of patients At the beginning of follow-up	Censored	Patients with outcome	Cumulative Incidence (95%CI)
1	59,887	4563	681	1.17 (1.09-1.27)
2	54,643	7042	234	1.63 (1.52-1.74)
3	47,367	6795	118	1.90 (1.78-2.020
4	40,454	7267	83	2.12 (2.00-2.46)
5	33,104	6955	64	2.33 (2.20-2.46)
6	26,085	6210	48	2.54 (2.39-2.69)
7	19,827	5504	28	2.69 (2.53-2.85)
8	14,295	5013	25	2.90 (2.72-3.08)
9	9257	3874	16	3.11 (2.91-3.31)
10	5367	3134	7	3.29 (3.05-3.53)

Table 4.5 Mesh Revision/ Removal After Mesh-Based Surgery for SUI Based on Provider' Surgical Volume

	High-volume Surgeons (n=44,140)	**Low-volume Surgeon (n=15,747)**
Duration of follow-up, median, (IQR), years	4.5 (2.38-6.96)	4.24 (2.24-6.68)
Total follow-up, person-years	210,483	72,318
Outcome, No. of patients, %	890 (2.0)	417 (2.6)
Time from index date to outcome, median (IQR), years	0.94 (0.34-2.59)	0.93 (0.35-2.38)
Event rate per 1000 patient-years of follow-up (95% CI)	4.23 (3.96-4.52)	5.77 (5.24-6.35)
Unadjusted risk ratio (95% CI)	1 (Reference)	1.37 (1.17-1.49)

Multivariable analyses showed similar results regarding primary exposure (Table 4.7). With Hazard ratio of 1.37 (95% CI, 1.21-1.55; P value <0.01), patients who were operated on by low volume surgeon were more likely to have a later surgery to remove or revise the mesh. No significant difference was found between gynecologists and urologists in such risk (HR, 0.94; 95%CI, 0.83-1.08; P value, 0.38).

As we explained in our methodology, we adjusted for age, obesity, diabetes, concomitant hysterectomy, prior hysterectomy and non-mesh-based surgery for POP, concomitant non-mesh-based surgery for POP and hospital type. Those factors were considered as potential confounders.

Table 4.6 Mesh Revision/ Removal After Mesh-Based Surgery for SUI Based on Surgeon' Specialty

	Urologists (n=25,594)	Gynecologists (n=33,970)
Duration of follow-up, median, (IQR), years	4.96 (2.68-7.46)	4.10 (2.13-6.38)
Total follow-up, person-years	131,036	150,074
Outcome, No. of patients, %	584 (2.3)	712 (2.1)
Time from index date to outcome, median (IQR), years	1.0 (0.32-2.82)	0.90 (0.37-2.23)
Event rate per 1000 patient-years of follow-up (95% CI)	4.46 (4.11-4.83)	4.74 (4.41-5.11)
Unadjusted risk ratio (95% CI)	1 (Reference)	0.92 (0.82-1.02)

Table 4.7 Multivariable Survival Analysis to Assess Patients and Surgeon Risk Factors For Removal or Revision of Synthetic Sling after SUI

Variable	HR (95 CI%)	P value
Surgeon Volume		
High	1 (Reference)	
Low	1.37 (1.21-1.55)	<0.01
Surgeon Specialty		
Urology	1 (Reference)	
Gynecology	0.94 (0.83-1.08)	0.38
Multiple mesh-based procedures for SUI	4.73 (3.62-6.17)	<0.01
High risk patients [a]	0.58 (0.08-4.13)	0.59
Age per 10 years increase	0.86 (0.82-0.92)	<0.01
Obesity	0.82 (0.62-1.10)	0.19
Diabetes mellitus	1.11 (0.94-1.32)	0.22
Concomitant	1.24 (1.08-1.42)	<0.01

Variable	HR (95 CI%)	P value
hysterectomy		
Concomitant non-mesh-based surgery for POP	0.80 (0.66-0.97)	0.02
Academic/ Teaching hospital	1.18 (1.02-1.36)	0.03

Abbreviations: SUI, stress urinary incontinence; POP, pelvic organ prolapse.
[a] Includes patients with history of fistula, diverticulum, urethral injury, or radiotherapy

As per our secondary exposures, patients at higher risk for sling removal or revision were grouped together and analyzed. We had a total of 73 patients with the following high-risk features: history of urethral diverticulum or injury, history of urinary fistula, and history of prior pelvic radiotherapy. They did not show increase risk for sling removal or revision surgery (HR, 0.58; 95%CI, 0.08-4.13)

Concomitant hysterectomy at the time of sling implant for SUI did increase patient' risk for reoperation for sling revision or removal as outlined in table 4.7. However, non-mesh-based POP repair decreased the risk of reoperation for a later complication, (HR, 0.80; 95%CI, 0.66-0.97).

A total of 1,252 patients had multiple synthetic slings implants for SUI, and multivariable analysis showed significant increase in their risk for mesh removal or revision (HR, 4.73; 95%CI, 3.62-6.17; p <0.01).
Finally, patients who had their SUI procedure in teaching hospital were more likely to have their mesh removed or revised (HR, 1.18; 95%CI, 1.02-1.36; p= 0.03).

5 DISCUSSION

SUI in women will remain a substantial problem with significant social and economical impact. Surgical intervention based on the concept of strengthening urethral tissue and pelvic floor muscles was tried as early as 1900s when Von Giordano used a muscle graft to support urethra (2). Currently, as discussed in chapter one, synthetic sling or mesh-based procedure has become the gold standard management for treating SUI in female (1). However, this procedure is not without complications, for which many studies were done and lot of reviews were carried out to outline and predict those complications and estimate their incidence rate in different setups. Our study was designed to measure the incidence rate of reoperation for mesh-based complications and to study the effect of certain prespecified factors, which were hypothesized to influence the risk of complications.

5.1 Principal Findings

In our large cohort study, we found that rate of removal or revision of synthetic sling implanted for SUI was 2.2%, with a cumulative incidence rate of 3.29% at 10 years of the initial procedure. As one of important presumed predictors, surgeon' specialty (urology or gynecology) was evaluated, and our study showed that it has no effect on rate of reoperation for complications. Another important factor we assessed was the surgical volume of the operating surgeon, which did have an effect on the rate of

mesh removal or revision, with low-volume surgeon having 37% higher risk of reoperation on their patients. Other worthwhile findings about predictive factors were as following; first, our study showed that implantation of more than one synthetic sling increased the risk of complications by almost 5 folds compared to single synthetic sling implantation. Second, we found that concomitant hysterectomy did increase the risk of reoperation for mesh-related complications, however non-mesh-based POP surgery did not. Third, patients who had their operation in an academic or teaching hospital were more likely to have mesh-related complications. Finally, patients with known risk factor for following complications after implantation of synthetic sling, such as history of urethral injury or diverticulum, or had previous pelvic radiotherapy did not express more risk for sling removal or revision.

5.2 Comparison with Previous Studies

Conducting literature review for incidence rate for sling revision or removal after SUI surgery was challenging as most of authors reported incidence rates that were specific to certain reasons only like voiding dysfunction rather than the incidence rate in general (49). Others would only report cases series of sling removal due to different causes (50). One population-based cohort study did assess long-term incidence rate of sling revision for mesh erosion and urinary retention (51), and incidence rate of sling revision in their study was consistent with our reported one, with a cumulative risk of 3.7% at 9 years follow-up. Another case-control study carried out in US examined all women who underwent midurethral sling placement for SUI between January 2003 and December 2013 (52). Authors reported that 2.7%

of their patients underwent sling revision for different reasons, which is also close to incidence rate in our study.

As both urologists and gynecologists are involved in the management of SUI in females, both specialties had carried out placement of mid-urethral slings since synthetic sling appearance in late 1990s. Both specialties have different training curriculum related to pelvic surgery due to the obvious variation in daily practice. Studies had suggested differences between the two specialties in the surgical management of SUI and outcome of synthetic sling surgery (53), however, two studies showed no difference in incidence of sling revision or urological and non-urological complications (54) (53). Our study confirmed such finding, which emphasize the importance of procedure-based training rather than surgical background and training. It also supports the concept of similar basic surgical training programs or courses for trainees from both specialties in the aspect of sling-based surgery.

Volume-outcome relationship in health care has been evaluated and assessed in several studies (55) (56) (57). Authors in those studies concluded that for a numerous surgical procedures and medical conditions, higher volume (whether assessed in relation to hospital or physicians) was linked to better health outcomes. The strongest associations were found for acquired immune disease syndrome (AIDS) treatment and for cancer-related procedures like pancreatic cancer and esophageal cancer. Also the outcome of abdominal aortic aneurysms surgery, and pediatric cardiac diseases management was related to surgical volume (a median of 3.3 to 13 excess deaths per 100 cases were attributed to low volume) (56). In urology,

volume-outcome relationship have been also evaluated, mainly in uro-oncology procedures (58) (59) (60) (61) (62), with similar observation regarding the inverse relationship between volume of surgeons or hospitals and outcome measured by mortality rate, hospital stay, reoperation rate, or complication rate. For mesh-based surgery for SUI, the role of surgeons' surgical volume was not well assessed. One study assessed the surgeon' volume effect on complications rate in pubovaginal sling procedures carried out in US (63), where authors analyzed data from1356 patients underwent sling procedures, and investigated differences between the two groups of surgeons in surgical management of SUI in form of performing concomitant POP at the time of sling procedure and in rate of repeat anti-incontinence procedures and complications. They found that high-volume surgeons were more likely to perform simultaneous POP at the time of sling surgery. They also noticed that low-volume surgeons had higher reoperation rates to correct prolapse during the first postoperative year. However, both groups had no statistically significant difference in their rate of complications.

In our study, we did demonstrate a difference between high and low volume surgeons with a 37% increase risk for reoperation for mesh-related complications among low-volume surgeons. This supports the recent recommendations from both specialized surgeons and surgical societies of interest (64) (65), about the substantial need for adequate training in this subspecialist area and the importance of a thorough understanding of the relevant pelvic anatomy. Indeed, a review done by McLennan et al showed that a learning curve does exist for tension-free vaginal tape procedures (66). This was their conclusion after they evaluated 278 procedures done by 23 senior residents, and they assessed the rate of bladder perforation among

patients. They found that incidence of perforation inversely related to the number of cases performed. This shows the effect of increased number of procedures performed (i.e. surgical volume) in the placement of SUI slings and the complications rate (in more generalized view).

The assessment of different risk factors for mesh late complication after placement of synthetic slings was reviewed widely in the literature in relation to different surgical approaches and different surgical kits used. One important factor was the placement of another synthetic sling to treat recurrent SUI, and we did notice general acceptance of such practice in different reviews and studies (67) (68) (69) (70). However, authors of those studies did not investigate reoperation rate for late complication with long-term follow-up, which we think is an important influencing factor in choosing appropriate management approach for recurrent SUI. In our study, multiple synthetic slings (more than one) were placed in more 1300 patients, and this increased their risk of undergoing another surgery for mesh-related complications by almost 5-fold. We hope that enthusiastic surgeons will consider our finding before they place a second or even third synthetic sling when managing recurrent SUI. We won't recommend stopping this practice of placing multiple synthetic sling in patients who failed their primary surgery; we do advise careful patients selection and thorough counseling with them about potential risks, so patients are aware of all possible complications and do participate in this decision. We also agree with the recommendation to conduct multicenter, randomized clinical trials to look at the management of recurrent SUI and the tools used to assess patients before another surgical management (70).

An interesting finding in our study was the inverse relationship between age of patients and their risk for reoperation for mesh-related complication. Increased age is not considered a contraindication for mid-urethral sling placement for SUI; in fact a group of investigators from US analyzed data on national level of women underwent SUI surgery from 1979 to 2004. They found that the most significant increase in frequency of procedures was among the population of patients age >52 years (71), which was attributed to the fact of aging population and increase in number of women seeking care for incontinence. Studies comparing outcome of mesh-based surgery for SUI in elderly women compared to young women showed contradictory results (72) (73) (74) (75) (76). However, no well-conducted review with an appropriate long period follow-up assessed age as predictor factor for mesh-related complication surgery. In our study, median age among cohort patients was 53 years, and risk for reoperation for complication was significantly decreased with each 10 years increment. This can be explained readily in the context of reasons for mesh revision or removal. Mesh erosion is a common reason for mesh removal, and reports of conservative management in literatures are sparse (2). Clinically, dyspareunia, vaginal discharge, and lower urinary tract symptoms are prevalent symptoms, and as older women tend to be less sexually active, this makes them less likely to experience such symptoms; they may not seek aggressive surgical management as a younger women might. Voiding difficulty or urinary retention is another important cause for mesh revision. It's usually managed initially conservatively with temporary catheter drainage, clean intermittent catheterization and timed voiding. However, if persistent, it needs revision. Older women may be more tolerant of a degree of urinary obstruction

compared to younger women, thus prompting more revisions in the younger population for this reason.

Concomitant hysterectomy at the time of SUI sling surgery did increase risk of reoperation due to mesh-related complication in our study. In the literature, concomitant hysterectomy at the time of sling placement for SUI was assessed as an influencing factor on the outcome of sling surgery, not on later complications, and many studies had found no such influence(77) (78) (79). However, the group from US who studied different predictors for sling revision found that concomitant hysterectomy actually decreased risk of sling revision (51). No other studies evaluated this variable. We think that both results could be explained via surgical techniques and the nature of tissues and their healing; however, as urologists do not perform concomitant hysterectomy, we think that such predictors would not affect long term results and complications of slings placement procedures performed by urologists, and deserves more assessment.

An unanticipated finding in our study was the effect of facility in which synthetic sling was implanted in on long-term risk for reoperation for complication. Having sling implanted in an academic teaching hospital raised the risk for a later removal or revision of that sling. The role of teaching hospitals in training residents and medical students especially when they are university-affiliated centers is paramount. Surgical residents and students are involved with varying degrees in performing surgical procedures and in the care of patients. This is the argument for hiring clinicians with an academic background and competitive post-graduate training in teaching hospitals. Moreover, in the last two decades, teaching

hospital gained increased attention in national policy plan world-wide, and several studies investigated the relationship between teaching centers and quality of health care provided, measured by mortality rate, length of stay, perioperative complications, and morbidity. For example, three studies done in US evaluated mortality as a marker of quality of care, and it's relationship to teaching status of the facility serving patients in the field of cardiovascular diseases (80) (81) (82), and all three studies showed lower mortality rate in the cases treated in teaching hospitals. Other studies assessed this relationship in major complex surgeries related to cancer, and they had similar findings (83) (84). However, when it comes to more confined surgeries like abdominal hysterectomy done for benign conditions and rectal cancer surgery, studies showed no significant difference in mortality between teachings versus non teaching hospitals (85) (86). In mesh-based surgery for SUI, no studies were found evaluating this relationship, apart from one done in Taiwan (87), where they assessed type of facility (medical center, regional, and local hospitals) on reoperation rate after SUI procedures, and they found no significant differences between all three different hospitals. This finding was attributed by the investigators to hospital' volume rather than teaching status of it. In our study, such difference in reoperation for mesh-related complications could be explained by several factors. First, patients referred or treated in teaching hospital usually are those with multiple comorbidities, which may increase their original risk for complications. Second, as teaching hospitals usually cover wider geographical region, their patient-volume would be bigger than those of community non-teaching hospitals. Third, ongoing residency program in teaching hospitals usually are more busy and packed with residents, who may have higher morbidity rate in outcome of surgical procedures (88).

Lastly, in our study patients considered to be at higher risk of reoperation for mesh-related surgery did not in fact demonstrate a higher risk. Prior pelvic radiotherapy, history of urethral injury or diverticulum, and prior urinary fistula are all theoretical predisposing factors for later complications after synthetic sling placement because they affect tissue healing and reaction to foreign body, although this is based primarily on experts' opinion. Our results can be explained by the small number of patients with those predisposed risk factors, which makes it even harder for future study and better evaluation. Such results won't change urologists or gynecologists' daily practice of avoiding synthetic sling placement in this subset of patients, but it may encourage them to apply the concept of sling placement in highly selected patients when they have such presumed risk factors.

5.3 Strength and Limitations

Our study has evaluated a large number of patients who underwent SUI surgery for the risk of reoperation for mesh-related complication. It has a long follow-up period to document such complication-related operations.

We analyzed a data for almost 60,000 patients with synthetic sling implants, with comprehensive data about their baseline criteria, their attending surgeon' specialty, and their attending surgeon' experience measured as surgical volume. This is a credit to the nature of administrative database in Ontario, Canada, which was examined and assessed as we explained in

methodology chapter. Moreover, due to the unique health care system in Canada, and the accessibility of different people to one-government-based medical facilities with different surgeons, from which we got our data, we can generalize our findings in a more reassured manner.

Finally in our study, we assessed several the effect of covariates that were not evaluated in literature previously, which may help in understanding different risk factors for mesh-related complications and improve patients counseling for synthetic sling placement. This is important in the current view of the multiple FDA notifications and ongoing lawsuits in US and Canada.

Our study was limited by the following: first, outcome was measured by surgical intervention, so we only documented mesh-related complications that were treated via surgical intervention. Thus, we likely underestimated complications related to mesh that were treated conservatively. Second, we could not identify type or severity of incontinence before primary surgery in order to study its possible relationship with reoperation rate and its risk. Third, there was no information about different types of surgical kits that were used in sling implant, and different surgical techniques like retropubic or transobturator placement of the sling could not be identified. So, their presumed effect on the incidence rate of reoperation for mesh-related complication could not be evaluated. Fourth, detailed reasons for which slings were removed or excised were not available in all patient' data. This was due to the nature of coding system for surgical procedures.

5.4 Future Research

Our study found no difference between urologists and gynecologists in reoperation for complications after synthetic sling placement for SUI, which is a common entity that is treated by both specialties. This might be the basis for further studies and evaluation of other common surgical practice, which can facilitate mutual training program that can accept candidates from both specialties with focusing on procedure-based surgical skills rather than their unique daily practice.

The effect of certain rare variables on reoperation after synthetic sling placement needs more evaluation on. Multicentric assessment for example can overcome the rarity of such variables and can provide more comprehensive information on them.

Finally, academic and teaching hospitals play an important role in training clinicians and equip different medical, regional, and local community hospitals with surgeons who should be ready to practice independently. For this, we think that further studies of different processes of care in teaching hospital is vital at all dimensions, in order not to compromise health care provided to population in our pathway of training future providers.

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Appendix A: List of Abbreviation

AIDS	Acquired Immune Deficiency Syndrome
BMI	Body Mass Index
CCI	Canadian Classification of health Intervention
CI	Confident Interval
CIHI	Canadian Institute for Health Information
CJD	Creutzfeldt-Jakob Disease
DAD	Discharge Abstract Database
DM	Diabetes Mellitus
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICD	International Classification of Diseases
ICES	Institute for Clinical Evaluative Sciences
ICS	International Continence Society
IQR	Interquartile range
ISD	Intrinsic Sphincteric Dysfunction
IUGA	International Urogynecological Association
LUTS	Lower Urinary Tract Symptoms
MAUDE	Manufacturer and User Device Experience
MUS	Midurethral Sling
OAB	Overactive Bladder
OHIP	Ontario Health Insurance Plan
POP	Pelvic Organ Prolapse
PVS	Pubovaginal Sling

RMUS	Retropubic Midurethral Sling
SDM	Standardized difference of the mean
SDS	Same Day Surgery
SIS	Small Intestine Submucosa
SUI	Stress Urinary Incontinence
TMUS	Transobturator Midurethral Sling
TOT	Transobturator Tape
TVT	Tension-free Vaginal Tape
UDS	Urodynamic Study
US	United States
UTI	Urinary Tract Infection

Appendix B

CCI Codes Used in Identifying Synthetic (Mesh-Based) SUI Procedures in OHIP and CIHI-DAD/SDS Databases (Cohort Patients)

CCI Code	Dates Active	Description	Number of patients in cohort
1PL74AFFF	April 2002-March 2006	Fixation, bladder neck combined open abdominal and endoscopic transvaginal approach using tension free vaginal tape [TVT] technique	2913
1PL74AFXXN	April 2002-Present	'Fixation, bladder neck combined per orifice (vaginal) and open (abdominal) approach using synthetic material	3677
1PL74AFXXQ	April 2003-Present	'Fixation, bladder neck combined per orifice (vaginal) and open (abdominal) approach using combined sources of tissue [e.g. graft and synthetic tissue]	66
1PL74ALFF	April 2002-March 2006	Fixation, bladder neck combined percutaneous and vaginal approach using tension free vaginal tape [TVT] technique	11535

CCI Code	Dates Active	Description	Number of patients in cohort
1PL74ALXXN	April 2006-Present	Fixation, bladder neck combined per orifice (vaginal) and percutaneous approach using synthetic material (e.g. TVT technique)	32268
1PL74CRXXN	April 2009-Present	'Fixation, bladder neck per orifice (vaginal) approach with incision using synthetic tissue (e.g. TVT technique)	7932
1PL74DAXXN	April 2009-Present	'Fixation, bladder neck endoscopic (laparoscopic) (retropubic) approach using synthetic tissue	549
1PL74LAXXN	April 2006-Present	Fixation, bladder neck open (retropubic, perineal) approach using synthetic material (sling)	933
1PL74LAXXQ	April 2006-Present	Fixation, bladder neck open (retropubic, perineal) approach using combined sources	14

Appendix C

CCI Codes Used to Define Primary Outcome

CCI Code	Dates Active	Description
1PL54CAXXN	April 2006-Present	Management of internal device, bladder neck of synthetic urethral sling (tension free vaginal tape [TVT]) using per orifice [vaginal] approach
1PL54LAXXN	April 2006-Present	Management of internal device, bladder neck of synthetic material (urethral sling) (tension free vaginal tape [TVT]) using open approach
1PL55CAXXN	April 2006-Present	Removal of device, bladder neck of synthetic urethral sling [tension free vaginal tape] using vaginal approach
1PL55LAXXN	April 2006-Present	Removal of device, bladder neck of synthetic urethral sling [tension free vaginal tape] using open approach
1PQ56BA	April 2002-Present	Removal of foreign body, urethra using endoscopic per orifice (transurethral) approach
1PQ56CA	April 2002-Present	Removal of foreign body, urethra using per orifice approach
1PQ56DA	April	Removal of foreign body, urethra using

CCI Code	Dates Active	Description
	2002-Present	endoscopic (percutaneous) approach
1PQ56LA	April 2002-Present	Removal of foreign body, urethra using open approach (abdominal, perineal)
1PQ56QY	April 2002-Present	Removal of foreign body, urethra using open transvaginal approach
1PQ57BAGX	April 2002-Present	Extraction, urethra using endoscopic per orifice approach (transurethral) and device NEC [e.g. forceps, meatome]
1PQ57LAAM	April 2002-Present	Extraction, urethra using open approach and basket device
1PQ57LAGX	April 2002-Present	Extraction, urethra using open approach and device NEC [e.g. forceps, meatome]
1PQ59BAAG	April 2002-Present	Destruction, urethra endoscopic per orifice approach using laser
1PQ59BAAZ	April 2002-Present	Destruction, urethra endoscopic per orifice approach using ultrasonic probe
1PQ72AC	April	Release, urethra using combined open

CCI Code	Dates Active	Description
	2002-Present	abdominal with vaginal approach
1PQ72LA	April 2002-Present	Release, urethra using open approach
1PQ72PK	April 2002-Present	Release, urethra using open retropubic approach
1PQ72QY	April 2009-Present	Release, urethra using open transvaginal approach
1PQ72QYAG	April 2002-Present	Release, urethra using open transvaginal approach and laser
1PQ86MB	April 2002-Present	Closure of fistula, urethra simple excision and closure terminating at skin (urethrocutaneous, urethroscrotal, urethroperineal)
1PQ86MD	April 2002-March 2009	Closure of fistula, urethra NEC simple excision and closure terminating in genital tract [urethrovaginal]
1PQ86MH**	April 2009-	Closure of fistula, urethra simple excision and closure terminating in genital tract

CCI Code	Dates Active	Description
	Present	[urethrovaginal]
1RS55CAXXN	April 2003-Present	Removal of device, vagina of synthetic material (e.g. mesh, sling) using per orifice approach
1RS55LAXXN	April 2002-Present	Removal of device, vagina of synthetic tissue (e.g. mesh) using open approach
1RS56CA	April 2002-Present	Removal of foreign body, vagina using per orifice [vaginal] approach (for simple extraction)
1RS56CR	April 2002-Present	Removal of foreign body, vagina using per orifice [vaginal] approach and incisional technique
1RS56DA	April 2006-Present	Removal of foreign body, vagina using endoscopic (laparoscopic) approach
1RS56LA	April 2006-Present	Removal of foreign body, vagina using open (abdominal) approach
1RS86LAXXE	April 2002-March 2006	Closure of fistula, vagina NEC terminating at skin, using open (perineal) approach and local flap repair
1RS86MB	April	Closure of fistula, vagina for fistula

CCI Code	Dates Active	Description
	2006-Present	terminating at skin (vaginal, perineal) and simple apposition (suturing) for closure
1SZ55LAXXN	April 2002-Present	Removal of device, soft tissue of the chest and abdomen of mesh using open approach

Appendix D

CCI Codes Used to Identify Study Covariates

Covariate	Source	Codes
Obesity	OHIP CIHI-DAD/SDS (ICD 10) CIHI-DAD/SDS (ICD 9)	E676, E010 E66x Obesity 278.x Obesity
Pelvic organ prolapse repair (with or without mesh)	CIHI-DAD/SDS (CCP*)	82.40 Anterior & Posterior repair 82.41 Anterior repair 82.42 Posterior repair 82.43 Anterior & Posterior Repair 81.30 Repair of uterine support 81.31 Interposition 81.32 Other uterine suspension 81.33 Vaginal repair chronic uterine inversion 81.39 Other repair of uterine support
Pelvic organ prolapse repair (with mesh)	CIHI-DAD/SDS (CCI)	1RS80CRXXN Synthetic repair vagina (Vaginal approach) 1RS80CAXXN Synthetic repair vagina 1RS80LAXXN Synthetic repair vagina, (abdominal approach) 1RS80DAXXN Synthetic repair vagina (MIS

Covariate	Source	Codes
		approach) 1RS80CRXXQ Repair vagina combined source 1RS80CAXXQ Repair vagina combined source 1RS80LAXXQ Repair vagina retropubic combined tissue source 1RS74CRXXN Repair vagina with synthetics 1RS74LAXXN Abdominal repair vagina with synthetics 1RS74DAXXN Repair vagina synthetics Lap 1RS74CAXXN Fixation vaginal approach with mesh
Any prolapse repair	OHIP	S716 S717 S718 S719 S723 S720 S721 S722 S812 S760 S813 S761 S758 S759
	CIHI-DAD/SDS (CCI)	1RS74 Fixation vagina 1RS80 Repair vagina
	CIHI-DAD/SDS (CCP)	82.40 Anterior & Posterior repair 82.41 Anterior repair 82.42 Posterior repair 82.43 Anterior & Posterior Repair 81.30 Repair of uterine support 81.31 Interposition

Covariate	Source	Codes
		81.32 Other uterine suspension 81.33 Vaginal repair chronic uterine inversion 81.39 Other repair of uterine support
Prior possible mesh based SUI procedure	CIHI-DAD/SDS (CCP)	71.40 Suprapubic sling operation 71.60 Periurethral suspension and compression
Urologic visit	OHIP	A355, C355, W355, A356, C356, W356, A353, C353, C354, A354
Gynecologic visit	OHIP	A205 A206 A203 A204 C205 C206 C203 C204 W305 W306
Hysterectomy	OHIP	S757 S816 S763 S762 S710 S758 S759
	CIHI-DAD/SDS (CCI)	5CA89CK Vaginal Hysterectomy with pregnancy 5CA89GB MIS hysterectomy with pregnancy 5CA89WJ Open hysterectomy with pregnancy 5CA89WK Open hysterectomy with pregnancy 5MD60KE Cesarean section hysterectomy 5MD60RC Cesarean section hysterectomy with forceps 5MD60RD Cesarean section hysterectomy with vacuum

Covariate	Source	Codes
		1RM89 Total hysterectomy 1RM91 Radical hysterectomy
	CIHI-DAD/SDS (CCP)	86.42 Hysterectomy with pregnancy 80.30 Total abdominal hysterectomy 80.40 Vaginal hysterectomy 80.50 Radical hysterectomy 80.60 Radical vaginal hysterectomy
High risk mesh patient: Prior fistula	CIHI-DAD/SDS (CCI)	1PQ86MH Urethrovaginal fistula excision and closure 1PQ86MD Urethrovaginal fistula excision and closure 1PQ86MB Urethral fistula excision and closure 1RS86MB Vaginal fistula closure 1RS86CAXXE Vaginal fistula closure 1RS86LAXXE Vaginal fistula closure
	OHIP	S709A, S523A, S524A
	CIHI-DAD/SDS (CCP)	70.33 Closure of fistula to urethra
High risk mesh patient: Prior urethral	CIHI-DAD/SDS (CCI)	1PQ87QY Partial excision urethra

Covariate	Source	Codes
diverticulum		
	CIHI-DAD/SDS (CCP)	70.20 Excision or destruction of urethral lesion 82.52 Vaginal reconstruction diverticulum
	OHIP	S541
High risk mesh patient: Prior radiation therapy	CIHI-DAD/SDS (CCI)	1PQ27JA Radiation urethra, external beam 1PM27JA Radiation bladder, external beam 1RM26 Radiation uterus, brachytherapy 1RM27JA Radiation uterus, external beam 1RZ27JA Radiation female genital tract 1RN26 Radiation cervix, brachytherapy 1RN27 Radiation cervix, external beam 1NQ27JA Radiation rectum, external beam 1NT26CA/HA/LA Radiation anus, brachytherapy 1NT27JA Radiation anus, external beam 1RB27JA Radiation ovary, external beam 1RS26 Radiation vagina, brachytherapy 1RS27JA Radiation vagina, external beam
High risk mesh patient: Prior urethral	CIHI-DAD/SDS ICD10	S37.3 Injury of urethra

Covariate	Source	Codes
injury		
	CIHI-DAD/SDS ICD9	867.0 Injury bladder or urethra 867.1 Open injury bladder or urethra

Curriculum Vitae

Hanaa Mohammed Al-Hothi

Post Graduate Training:

- January 2014- April 2015: Clinical fellowship in London Ontario- Canada in Voiding Dysfunction- Urology

- July 2007- May 2011: Resident in Arab Board of Health Specializations (ABHS) Urology Program, Doha- Qatar

- October 2004- June 2007: Resident in Surgical departments, Hamad General Hospital, Doha-Qatar

- September 2003- August 2004: Intern in Hamad General Hospital, Doha-Qatar

Post-Secondary Education:

- 2014- 2015: Master of Surgical Science (Candidate) -Western University, London- Ontario, Canada

- 2007-20011: Arab Board of Health Specializations (ABHS) Urology Program, Doha- Qatar

- September 1997 – July 2003: Medical Colleague in King Faisal University (Dammam University) in Kingdom of Saudi Arabia

Committees:

2012- Current: Core faculty in Urology Section- Surgery Department, Hamad General Hospital, Doha -Qatar

2012- Current: Member in Clinical Competency Committee in Urology Section- Surgery Department, Hamad General Hospital, Doha -Qatar

February 2012- May 2012: Internal Review Committee for Accident & Emergency Department, Hamad General Hospital, Doha -Qatar

October 2009- November 2011: Resident Council in Hamad Medical Corporation, Doha-Qatar

Researches:

- Complications of Vaginal Synthetic Slings in Women, Population-Based Cohort Study

- The Effect of Pelvic Fractures on Future Incontinence and Pelvic Organ Prolapse Surgery

- Prevalence & Risk Factors of Urinary Incontinence and it's influence on the Quality of life on female in Qatar

Publications:

- Welk B, Al-Hothi H, Winick-Ng J: Removal of Vaginal Mesh Used for the Treatment of Stress Urinary Incontinence. JAMA Surgery. 2015 September. 9:1-9

- Welk B, Al-Hothi H, Winick-Ng J: A Population Based Assessment of the Risk Factors for Mesh Removal or Revision After Female Incontinence Procedure. The Journal of Urology.2015 April; 193 (4).

- Welk B, Al-Hothi H, Winick-Ng J, Chou Q, MacMillan B, Lawendy AR. The effect of Pelvic Fractures on Future Stress Incontinence and Pelvic Organ Prolapse Surgery. Int Urogynecol J. June 2015; 26 (6).

- Ghafouri A, Alnaimi A, Al-Hothi H, Alroubi I, Alrayashi M, Molhim N, Shokeir A. Urinary Incontinence in Qatar: A study of the Prevalence, Risk Factors and Impact on Quality of life. Arab Journal of Urology. 2014 December; 12 (4).

Posters:

The effect of Pelvic Fractures on Future Stress Incontinence and Pelvic Organ Prolapse Surgery. Presented in Northeastern Section of the American Urological Association Meeting 2014, Amelia Island- Florida, USA