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FEMALE PELVIC FLOOR DISORDERS – OUTCOME AFTER MESH-AUGMENTED PROCEDURES AND STUDIES ON VAGINAL CONNECTIVE TISSUE

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To Mika, Juho and Aino

ABSTRACT

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Female pelvic floor disorders – outcome after mesh-augmented procedures and studies on vaginal connective tissue.

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Pelvic floor disorders, such as urinary incontinence (UI) and pelvic organ prolapse (POP), are common disorders in women. Because of the prolonged life expectancy the prevalence of UI and POP and the probability of ending up in surgery are increasing. However, the pathophysiology behind these disorders is still unsolved.

The aim of this thesis is to study possible alterations in the connective tissue in the vaginal wall in patients with and without POP. The long-term outcome and complications of mid-urethral slings (MUS) and mesh-augmented POP surgery were studied in heterogenic patient populations.

More elastin and a slight increase in immunostaining of type III and V collagens in tissue samples were obtained from patients with POP compared to controls in whom type I collagen was more prominent. The studies assessing the mesh-augmented procedures revealed good efficacy and high patient satisfaction after a long-term follow-up. Patients operated on because of mixed incontinence and with BMI >30 kg/m² reported significantly more urinary symptoms and a lower quality of life than the patients operated on because of stress urinary incontinence and the ones with BMI ≤30 kg/m². The objective outcome was equal between the groups. Mesh exposure through vaginal mucosa occurred in 23 % of the patients after POP surgery, most of these being asymptomatic.

There are alterations in connective tissues in patients with POP. Mid-urethral sling procedures produced good long-term cure rates and patient satisfaction. As to the prolapse surgery, in spite of relatively high exposure rate, mesh-augmented procedure proved to be safe and effective method for the correction of POP.

Keywords: connective tissue, elastin, collagen, female urinary incontinence, pelvic organ prolapse, incontinence surgery, mid-urethral tapes, polypropylene mesh, subjective outcome, objective outcome, mesh exposure

TIIVISTELMÄ

Pia Heinonen

Naisten lantionpohjan toimintahäiriöiden verkkoavusteiset leikkaukset ja muutokset sidekudoksessa

Turun Yliopisto, Lääketieteellinen tiedekunta, Synnytys- ja naistentautioppi, Turun Yliopiston Kliininen tohtoriohjelma; Turun yliopistollinen keskussairaala, Naistentaudit ja synnytykset, Turku, Suomi

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Lantionpohjan toimintahäiriöt, kuten virtsankarkailu ja laskeumat, ovat yleisiä ongelmia naisilla. Väestön ikääntymisen myötä niiden esiintymisen ja niistä johtuvien leikkausten lukumäärän odotetaan lisääntyvän. Toimintahäiriöiden yleisyydestä huolimatta niiden syntymekanismit tunnetaan huonosti.

Tämän väitöskirjatutkimuksen tarkoituksena on selvittää mahdollisia emättimen sidekudoksen muutoksia naisilla, joilla on laskeuma ja verrata tuloksia verrokkien sidekudokseen. Lisäksi tutkimme pitkän aikavälin seurannassa verkkoimplanttia käyttäen virtsankarkailun tai laskeuman vuoksi leikattujen naisten paranemista ja komplikaatioita heterogeenisissa potilasaineistoissa.

Laskeumapotilaiden sidekudoksessa havaittiin enemmän elastiinia. Laskeumapotilailla todettiin esiintyvän enemmän tyyppi III ja V kollageenia kuin verrokeilla, joilla tyyppi I kollageenia esiintyi enemmän. Verkkoimplanttia käyttäen saavutettiin hyvä leikkaustulos ja korkea potilastyytyväisyys pitkän aikavälin seurannassa. Sekamuotoisen virtsainkarkailun vuoksi leikatuilla sekä potilailla, joilla painoindeksi oli yli 30 kg/m², elämänlaatu oli merkittävästi huonompi ja virtsankarkailuoireet hankalammat kuin ponnistusvirtsankarkailun vuoksi leikatuilla sekä potilailla, joilla painoindeksi oli ≤30 kg/m². Objektiivinen paraneminen oli ryhmissä samanlaista. Verkon syöpymistä emättimen limakalvon läpi ilmeni 32 (23 %) potilaalla laskeumaverkkoleikkauksen jälkeen, ja näistä suurin osa oli oireettomia.

Laskeumapotilaiden sidekudoksessa havaittiin muutoksia. Virtsankarkailu- ja laskeumakirurgiassa käytettävät verkot ovat tehokkaita pitkän aikavälin seurannassa, ja potilastyytyväisyys on korkea. Oireeton verkon syöpyminen emättimen limakalvon läpi laskeumaverkkoleikkauksen jälkeen oli yleinen komplikaatio.

Avainsanat: sidekudos, elastiini, kollageenit, virtsankarkailu, virtsankarkailuleikkaus, polypropyleeniverkko, leikkaustulos, verkkoeroosio, gynekologiset laskeumat

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ABBREVIATIONS

AC	anterior colporrhaphy
BMI	body mass index
DIS	detrusor instability score
ECM	extracellular matrix
EQ-5D	EuroQoL-5D
FDA	Food and Drug Administration
IIQ	Incontinence Impact Questionnaire
MUI	mixed urinary incontinence
MUS	mid-urethral sling
PFDI	Pelvic Floor Distress Inventory
PISQ-12	Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire
POP	pelvic organ prolapse
POPDI	Pelvic Organ Prolapse Distress Inventory
POP-Q	Pelvic Organ Prolapse Quantification
SCP	sacrocolpopexy
SUI	stress urinary incontinence
TOT	transobturator tape
TVM	transvaginal mesh
TVT	tension-free vaginal tape
UDI	Urogenital Distress Inventory
UI	urinary incontinence
UISS	Urinary Incontinence Severity Score
UUI	urgency urinary incontinence
VAS	Visual Analogue Scale
VG	van Gieson

LIST OF ORIGINAL PUBLICATIONS

I Heinonen P, Söderström M, Lintunen M, Honka H, Järveläinen H, Kiilholma P, Ala-Nissilä S: Elastin and collagen in the vaginal wall of women with and without genital prolapse. Submitted.

II Heinonen P, Ala-Nissilä S, Kiilholma, P, Laurikainen E. Tension-free vaginal tape procedure without preoperative urodynamic examination: long-term outcome. Int J Urol 2012;19: 1003–1009.

III Heinonen P, Ala-Nissilä S, Räty R, Laurikainen E, Kiilholma P: Objective cure rates and patient satisfaction after the transobturator tape (TOT) procedure during a 6.5-year follow-up. J Minim Invasive Gynecol 2013; 20:1:73-78.

IV Heinonen P, Ala-Nissilä S, Aaltonen R, Kiilholma R: Trocar-guided polypropylene mesh for pelvic organ prolapse surgery—perioperative morbidity and short-term outcome of the first 100 patients. Gynecol Surg 2011; 8:165-170.

V Heinonen P, Aaltonen R, Joronen K, Ala-Nissilä S: Long-term outcome after transvaginal mesh repair of pelvic organ prolapse. Submitted.

1. INTRODUCTION

Pelvic floor disorders, such as genital prolapse and urinary incontinence (UI), are common diseases impairing the quality of life, causing social isolation and financial burden. An estimated risk for women to undergo surgery because of pelvic organ prolapse (POP) or UI by the age of 80 to 85 years is 11 %-19 % (Olsen et al., 1997; Smith et al., 2010). In addition, approximately 30 % of the patients undergo reoperation due to UI or POP within four years of the original surgery (Olsen et al., 1997). The prevalence of these diseases is increasing because of the prolonged life expectancy of the women and the change in the age structure of population.

Regardless of the frequency of pelvic floor disorders the pathophysiology behind it is unsolved. The composition of the fibrillar components of the connective tissue plays a crucial role determining the biomechanical properties of tissues. Alterations in the connective tissue of the women with UI and POP have been observed (Chen and Yeh, 2011). However, the results of the studies are not consistent. In order to develop the treatment modalities there is a need for further evaluation of the differences in the connective tissue among women with pelvic floor disorders.

Surgical treatment of UI and POP is planned in case of a failed conservative treatment. Mid-urethral slings are nowadays the main techniques used in the surgical correction of stress urinary incontinence. The data concerning the objective and subjective outcomes of the tension-free vaginal tape procedure is reassuring (Aigmueller et al., 2011). However, the impact of preoperative urodynamic studies on the surgical outcome is not clear (Jung et al., 2009). The outcome of transobturator tapes after three years of follow-up is convincing and the complication rates are low (Abdel-Fattah et al., 2012). Nevertheless, the data assessing the long-term outcome of the transobturator tape procedure is needed in order to verify its major role in UI surgery.

The introduction of the synthetic meshes in the vaginal repair of POP has expanded the surgical options. The aim for the development of vaginal mesh surgery was to diminish the high recurrence and reoperation rates occurring after traditional vaginal POP surgery (Jelovsek et al., 2007). The short-term anatomical outcome after trans-vaginal mesh is satisfying (Altman et al., 2011) but the long-term data is missing. The possible life-threatening intraoperative complications and relatively high mesh exposure rates raised the concern of the justification for the use of transvaginal mesh in POP surgery. In 2011 the US authority Food and Drug Administration (FDA) gave a warning considering the use of transvaginal mesh (FDA July 13, 2011). The long-term data regarding the efficacy and complications of this technique was necessitated.

In the present study the evaluation of long-term objective and subjective outcomes after three various mesh-augmented surgical procedures, such as tension-free vaginal tape, transobturator tape and transvaginal mesh, were performed. The long-term efficacy, anatomical results, adverse events and the subjective outcome and satisfaction of the patients were the primary points of interest. In order to clarify the complex pathophysiology of POP and UI the possible changes in the fibroelastic composition of the connective tissue of the vaginal wall together with the clinical factors were investigated.

2. REVIEW OF THE LITERATURE

2.1. Prevalence, etiology and pathophysiology of pelvic floor disorders

2.1.1. Prevalence of pelvic floor disorders

High life expectancy increases the number of women seeking help for pelvic floor disorder. The prevalence of symptomatic pelvic floor dysfunction was observed in 24 % of the patients older than 20 years in a cross-sectional nationwide study (Nygaard et al., 2008). According to a calculation there is going to be a 55 % increase in the number of women with urinary incontinence (UI) and a 46 % increase in the number of women with pelvic organ prolapse (POP) from 2010 to 2050 in the USA (Wu et al., 2009). The types and symptoms of UI and POP are presented in detail in a report of International Continence Society and the International Urogynecological Association (ICS/IUGA) (Haylen et al., 2010).

Prevalence of any type of UI is reported to be 12.8-49 % (Botlero et al., 2008; Minassian et al., 2008; Sandvik et al., 1993). The great variation of the reported prevalence results from the heterogeneity of the studies and the differences in the methodology used between reports. Prevalence of 29 % was reported in the study where the urinary incontinence severity index was designed (Sandvik et al., 1993). In a survey of 17,080 women in four European countries the prevalence of UI was 35 % (Hunskaar et al., 2004). However, only <5 % of these women had undergone surgery for SUI. The prevalence of UI increases with age and SUI is the most common type. Prevalence is the highest among middle-aged and elderly women (Botlero et al., 2008; Hunskaar et al., 2004; Minassian et al., 2008; Sandvik et al., 1993).

The prevalence of POP is reported to be 30.8-41 % (Hendrix et al., 2002; Samuelsson et al., 1999; Swift et al., 2005). However, only a minority of the patients is symptomatic (Nygaard et al., 2008; Swift et al., 2005). The natural history of POP is not fully understood. Symptomatic POP does not necessarily progress significantly over time. At some extent a certain degree of asymptomatic POP is considered normal in women at an older age (Bradley et al., 2007; Gilchrist et al., 2013) . The lifetime risk for a woman to undergo surgery for POP or UI is reported to be 11-19 % (Olsen et al., 1997; Smith et al., 2010).

2.1.2. Etiology and pathophysiology of pelvic floor dysfunction

The pathophysiology behind the pelvic floor dysfunction is not entirely solved. Essential for normal pelvic floor anatomy and function is the integrity of the connective tissue, muscles and ligaments composing the pelvic floor.

Advancing age is a significant risk factor for UI and POP (Hendrix et al., 2002; Miedel et al., 2009; Nygaard et al., 2008; Swift et al., 2005) and ageing is strongly related to persistent UI particularly (Devore et al., 2013). Along with ageing a gradual denervation of striated muscles leads to decreased volume and function also in the muscles of the levator ani complex possibly resulting in altered anatomical conditions of pelvic floor (Boreham et al., 2002).

Vaginal delivery increases the risk for POP increasing with the number of vaginal deliveries along with the birthweight of the infant (Gyhagen et al., 2013b; Hendrix et al., 2002; Nygaard et al., 2008; Swift et al., 2005). In addition, vaginal delivery is a risk factor for developing UI (Gyhagen et al.,

2013a; Rortveit et al., 2003). During vaginal delivery the striated levator muscles are stretched possibly causing damage to muscles and nerves (DeLancey, 2005). Pregnancy is an independent risk factor for pelvic floor disorder (Swift et al., 2005).

There is strong evidence to support the causal role of obesity in the development of UI (Osborn et al., 2013) and POP (Gyhagen et al., 2013b; Miedel et al., 2009; Nygaard et al., 2008). Fourfold risk for UI and significantly more severe UI symptoms have been associated with obesity (Chen et al., 2009). Obesity increases intra-abdominal pressure and may lead to the weakening of the pelvic floor innervation and musculature (Hunskaar, 2008). Even moderate weight loss reduces the UI symptoms probably by reducing the intra-abdominal pressure (Subak et al., 2009b). The risk for recurrence after POP surgery may increase in obese patients (Kawasaki et al., 2013). The data regarding obesity as a risk factor for POP is not entirely consistent, according the study which concluded that obesity was not a risk factor for prolapse but it had a significant effect on the severity of POP symptoms (Washington et al., 2010).

Previous hysterectomy, especially vaginal hysterectomy, may raise the risk for POP and UI (Forsgren et al., 2012; Swift, 2000). Vaginal hysterectomy increases the risk for a SUI procedure later on in life (Altman et al., 2007). Presumably, the women who had undergone vaginal hysterectomy had frequently had previous weakened pelvic floor with existing or imminent prolapse preoperatively.

Furthermore, there are other potential risk factors for pelvic floor dysfunction such as white race (Hendrix et al., 2002), menopause or oestrogen deficiency (Quiroz et al., 2012), neuropathy (Hill et al., 2008) and connective tissue disorders (Chen and Yeh, 2011). Smoking increases the risk for urinary urgency and MUI (Hannestad et al., 2003; Tähtinen et al., 2011), whereas its role as a risk factor for POP is not clear (Lonnée-Hoffmann et al., 2014).

Genetic factors inevitably increase the risk for pelvic floor dysfunction according to the studies regarding genetic influence on UI and POP (Altman et al., 2008; Lammers et al., 2012). In a Swedish registry study comparing the occurrence of POP and UI in female monozygotic and dizygotic twins the genetic effect was significant (Altman et al., 2008). However, the authors concluded that the effect of the environmental factors was substantial.

Elastin and collagen in vaginal wall

Connective tissue of the vaginal wall consists of non-fibrillar components, such as proteoglycans and glycoproteins, and fibrillar collagens and elastin. Collagens and elastin are responsible for the mechanical properties of the tissue. Degradation, synthesis, and remodelling of the fibrillar components of extracellular matrix enable the connective tissue to adapt and repair the damaged tissues after trauma. The vaginal wall is made up of four layers: a stratified squamous epithelium, a sub-epithelium, a layer of smooth muscle and adventitia. Sub-epithelium and smooth muscle layers form the fibromuscular layer, which represents the supportive tissue of the vaginal wall. The layers composing the vaginal wall are presented in Figure 1.

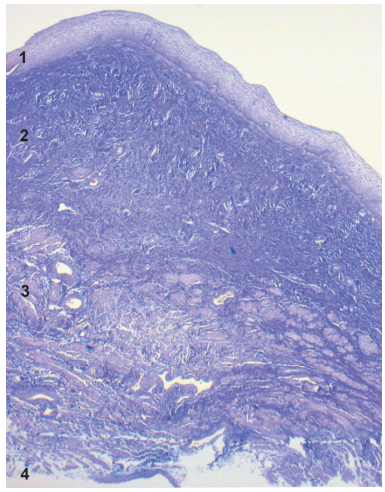


Figure 1. The layers composing the vaginal wall. 1=stratified squamous epithelium, 2=sub-epithelium, 3=smooth muscle, 4=adventitia

Elastin is laid down mainly during the third trimester of foetal life, and elastin fibre turnover is continuous only in the reproductive tract in the human body (Alperin and Moalli, 2006). Elastin fibre is able to stretch and return to its original length without damage providing elasticity, and to protect the integrity of tissues during mechanical stress. The vaginal wall contains large quantities of elastin to diminish tissue trauma during pregnancy, childbirth and to resist weight load of tissues caused by ageing or obesity.

Elastic fibre is a complex insoluble polymer that is impossible to extract from tissues in physiological conditions. Tropoelastin is secreted upon scaffold of microfibrils made of fibrillins (Kielty et al., 2002). Elastin is formed by the assembly of tropoelastin monomers followed by catalysis by lysyl oxidases (Kerkhof et al., 2009). Mature elastin is a macromolecule consisting of an elastin core surrounded by a mantle of fibrillin-rich microfibrils.

The data regarding histological changes in the patients with pelvic organ prolapse is not consistent. An increased content of tropoelastin, the precursor of elastin, and increased density of mature elastin have been observed in the vaginal wall of the women with POP compared to women without POP (Kerkhof et al., 2014; Lin et al., 2007; Zong et al., 2010). On the contrary, the study comparing the elastin density in the prolapsed and non-prolapsed vaginal wall tissue reported a decreased elastin density in the prolapsed site (de Landsheere et al., 2014). In addition, others found decreasing elastin gene transcription and elastin synthesis in women with POP and UI (Yamamoto et al., 1997). A decreased fibre width along with a decreased elastin expression have been reported in postmenopausal patients with a large cystocele compared to controls (Karam et al., 2007). Ageing alters the structures of elastic fibres resulting in diminished tissue elasticity (Sherratt, 2009).

The collagen family makes up one third of all the protein in the human body. At the primary structure level after a post-translational modification of lysine and proline, the alpha polypeptide chains are formed. The secondary structure is formed by the coiling of the alpha chains into right-handed alpha-helices. The tertiary structure is formed by the formation of the left-handed triple helix. The intracellular formation of the triple helix produces the long, rod-like structure of procollagen, which is excreted into the extra-cellular space (Ottani et al., 2002). After the self-

assembly procollagen forms fibrils, which as for form fibres and fibre bundles (Kerkhof et al., 2009). The combination of different alpha chains defines the type of collagen being formed.

Type I, III and V collagens are presented in the vagina and its supportive tissues (Kerkhof et al., 2009). Type I collagen is the most common collagen in the connective tissues and it forms the largest fibres providing the strongest tensile strength (Ottani et al., 2001). Type III collagen appears typically in the tissues incorporated with elastic properties and is the predominant collagen type in the connective tissue of the vagina. Type V collagen has an important role in the structure of extracellular matrix, fibrillogenesis and tissue repair. Its role in the vaginal wall is not clear (Kerkhof et al., 2009; Ottani et al., 2001).

The total collagen content has been reported to diminish in the patients with POP in the uterosacral ligaments (Gabriel et al., 2005) . Type I collagen expression has found to be decreased and type III collagen increased in the uterosacral ligaments of the patients with POP (Yucel et al., 2013; Zhao and Zhou, 2012). This was confirmed by others, who observed an increased type III collagen expression in the vaginal wall (Mosier et al., 2010). Others found a significantly increased total collagen content in the vaginal wall in the patients with POP caused mainly by the increase in collagen types III and V (Moalli et al., 2005). Opposite results were reported by authors who found a lower expression of type III collagen in the vaginal wall in women with POP (Lin et al., 2007).

2.2. Previous methods for incontinence surgery

The suburethral sling procedure was introduced in the beginning of last century. Numerous modifications followed during the following decades in order to improve the outcome and reduce complications. In 1949 Marshall, Marchetti and Krantz introduced a procedure where the bladder neck was suspended into the periosteum of symphysis pubis (Marshall et al., 2002). To avoid complications, such as osteitis followed by the attachment of the sutures in the periosteum, Burch described the technique where the anterior vaginal wall and the paravesical tissues were elevated by several non-resorbable sutures in the Cooper's ligament (Burch, 1961). This technique was later modified by using two resorbable sutures for both sides (Kiilholma et al., 1993). Colposuspension was regarded as the "gold standard" for treating SUI before the introduction of mid-urethral slings (MUS). In a study following patients for 10-20 years after Burch colposuspension the objective cure was satisfying, but declining for 12 years when a plateau of 69 % was reached (Alcalay et al., 1995). Less invasive needle suspensions revealed disappointing long-term cure rates (Moser et al., 2006).

2.3. Theories behind the development of mid-urethral slings and vaginal mesh surgery

In 1992 DeLancey introduced a model of the description of pathophysiology of POP based on a cadaver study (DeLancey, 1992). The pelvic floor support is divided into three levels. Level I (upper third of the vagina) is supported by sacrouterine and cardinal ligaments. Level II (middle third of the vagina) is laterally supported by arcus tendineus and fascia of the levator ani muscles. Level III (the lower third of the vagina) is integrated with the perineal membrane, the levator ani muscles and the perineal body. The appearance of the prolapse depends on the level of the collapsed support in the tissues reinforcing the vagina (Figure 2) (Barber, 2005).

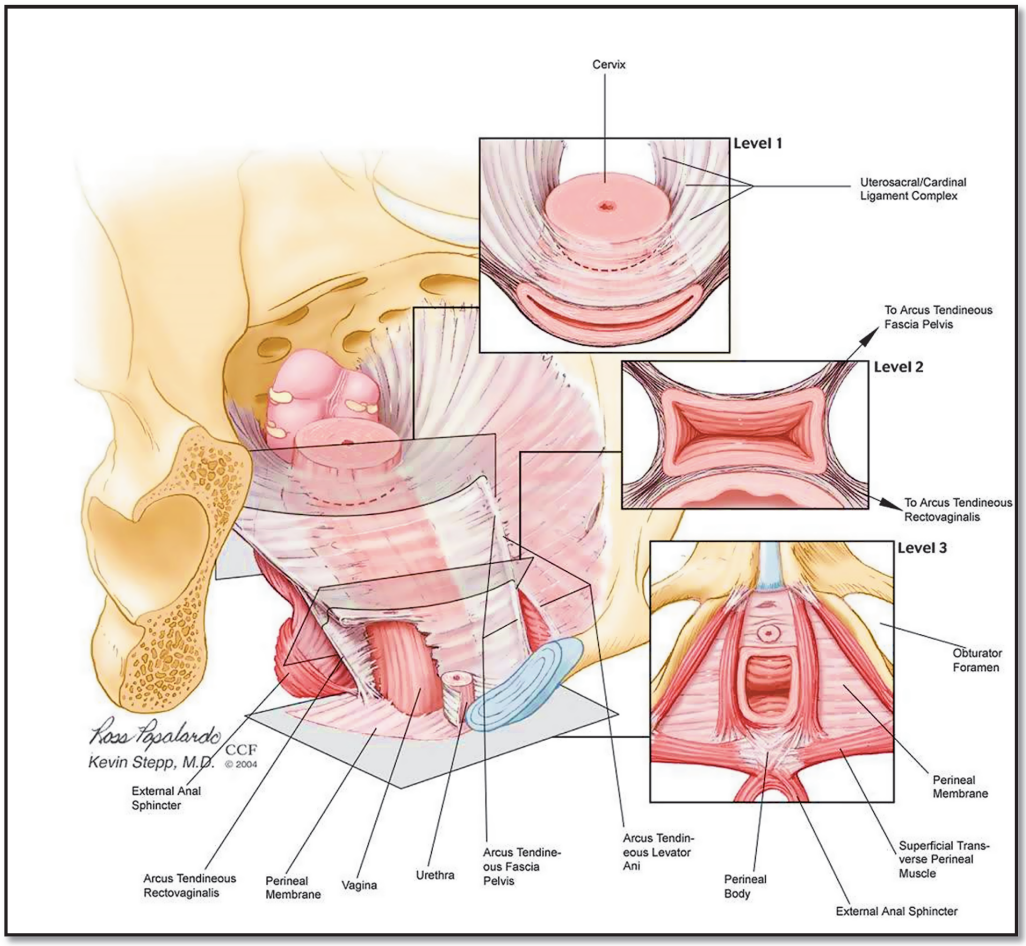


Figure 2. Integrated levels of support: illustration of the normal vaginal axis and the three levels of the support of the vagina and uterus from the perspective of a standing woman. Reprinted with permission, The Cleveland Clinic Center for Medical Art & Photography © 2014. All Rights Reserved.

In developing the modern incontinence surgery the focus was moved from supporting the urethrovesical junction to reinforcing mid-urethra. Mini-invasive procedures for the treatment of urinary incontinence are based on the integral theory introduced by Petros in 1993 (Petros and Ulmsten, 1993). According to this theory the pelvic brim is supporting the pelvic organs by three supporting ligaments: pubourethral, cardinal/uterosacral and arcus tendineus pelvis. The three muscle forces stretch and tension the organs to keep them in position and form. Damaged connective tissue ligaments and their supporting fascia may lead to the development of pelvic floor disorders, such as urinary or faecal incontinence, urgency, and frequency, and pelvic organ prolapses. Normal function may be achieved by restoring the normal opening and closing functions by reinforcing and replacing the stretched and damaged supporting ligaments.

2.4. Pelvic Organ Prolapse Quantification (POP-Q)

The POP-Q system (Bump et al., 1996) was introduced to add accuracy to the description of POP and standardise the terminology. It is an attempt to enable the comparison of the results more reliably between studies. It is widely accepted as a tool for research (Auwad et al., 2004). However, POP-Q has shown to be rather complicated in everyday clinical use.

The defined measurement points for POP-Q are the following: Aa measure describes the position of the point 3 cm proximal from urethral meatus and Ba the most distal position of any part of the upper anterior vaginal wall from the vaginal cuff to the point Aa. Posterior measurement points Ap and Bp are analogous to the anterior ones. Point C represents the most distal part of the cervix or vaginal cuff. Point D represents the location of posterior fornix and is left out in the case of previous hysterectomy. The measurements are performed during the Valsalva manoeuvre except when measuring total vaginal length (TVL). POP-Q measurements are expressed as centimetres.

The POP-Q measurement points are presented in figures 3 and 4.

Anterior wall Aa	Anterior wall Ba	Cervix or cuff C
Genital hiatus gh	Perineal body pb	Total vaginal length tvl
Posterior wall Ap	posterior wall Bp	Posterior fornix D

Figure 3. Three by three grid for recording quantitative description of pelvic organ support. Adapted and modified from Bump et al.(Bump et al., 1996)

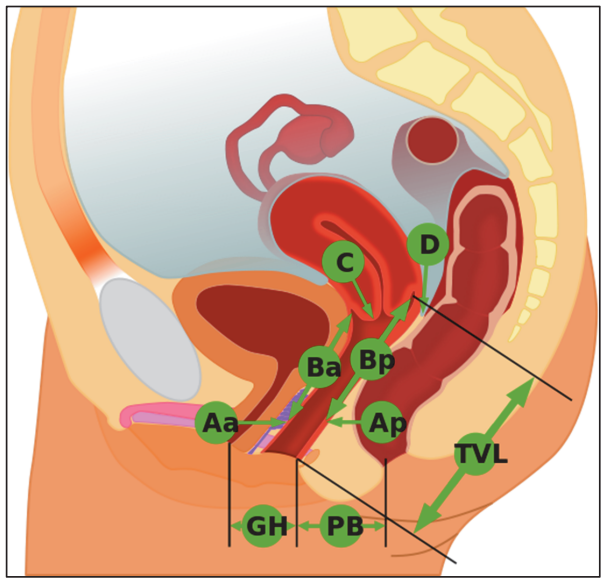


Figure 4. The POP-Q quantification. Reprinted with permission of Female_anatomy.svg: Tsaitgaistderivative work: Huckfinne (talk) - Female_anatomy.svg. Licensed under Creative Commons Attribution-Share Alike 3.0 via Wikimedia Commons

The staging of pelvic organ support by POP-Q consists of 5 stages:
Stage 0: no prolapse
Stage I: the most distal point of the prolapse is >1 cm above the level of the hymen.
Stage II: the most distal point of the prolapse is ≤1 cm proximal or distal to the level of the hymen.
Stage III: the most distal point of the prolapse is >1 cm below to the level of hymen and protrudes no further than 2 cm less than TVL.
Stage IV: total eversion of the lower genital tract.

2.5. Development of mesh and sling materials

The materials used in the incontinence and prolapse surgery have developed during the past two decades. Alterations in the patient's connective tissue, specifically elastin and collagens, may play important role for development of UI and POP. Possibly the repairs using native injured tissues may lead to insufficient support. The need for safe and biologically inert mesh materials has evolved along with the growing need for more efficient techniques in the incontinence and prolapse surgery.

The efficacy of absorbable or biological grafts, such as porcine dermis, solvent dehydrated cadaveric fascia lata, porcine skin collagen, bovine pericardium, and polyglactin in prolapse or incontinence surgery has shown not to be satisfying (Guerette et al., 2009; Guerrero et al., 2010; Hviid et al., 2010).

Insufficient results of absorbable graft materials led to the development of non-absorbable materials. There were numerous experiments from metallic grafts to nylon, polyester and Gore-Tex (expanded polytetrafluoroethylene). Polypropylene has shown to be a durable and flexible material for mesh surgery. Polypropylene mesh has proved to be biologically and chemically inert, which diminishes the risk for rejection (Cosson et al., 2003). Multifilament structure in grafts enhances the risk for infections and therefore monofilament meshes are generally used in surgery nowadays. Monofilament and macroporous polypropylene type I (class I) mesh seems to have the best mechanical qualities and the best tissue integration and is generally used in POP and incontinence surgery (Boukerrou et al., 2007).

2.5.1. Classification of meshes

The pore size is crucial when biological characteristics of the mesh materials are evaluated. If the interstices of the mesh are too small, bacteria are able to migrate and infiltrate whereas macrophages are too large to fit into the pores, thus allowing the possible infection to arise. Adequate pore size allows the rapid fibroplasia and angiogenesis in order to prevent bacterial contagion.

Amid classified the meshes in 1997 (Amid, 1997). The classification follows the pore size of the mesh.

Class I	Macroporous > 75 µm
Class II	Macro- with microporous < 10µm at least in one dimension
Class III	Microporous; with multifilament or microporous component
Class IV	Submicronic pores/sheets

Figure 5. The mesh classification by Amid (Amid, 1997)

Non-absorbable grafts may be multifilament, monofilament or composite, woven or knitted. Filaments can be twisted, coated braided and double braided. The contraction or shrinkage of the mesh may cause pelvic pain or dyspareunia. It may also have influence on the development of mesh exposure. The industry has generated different modifications as an attempt to avoid mesh contraction, such as adding absorbable components in the mesh or adding a collagen coating on the surface of the mesh (Milani et al., 2011; Rudnicki et al., 2013). At present the most common mesh used in the incontinence and prolapse surgery is a lightweight monofilament polypropylene mesh with pore size >75 µm.

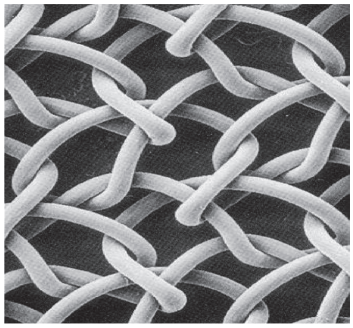


Figure 6. Polypropylene monofilament type I mesh, macroporous >75 µm. Reprinted with permission, Ethicon Surgical Care, Sommerville, NJ, USA

2.6. Urodynamic studies

Urodynamic studies (UDS) are used when there is a need for confirming the diagnosis of SUI and defining the type and severity of the urinary incontinence. UDS is an invasive study performed using a multichannel cystometry recording the intravesical pressure, voiding pattern and urethral function.

Preoperative UDS may be beneficial particularly if reoperation is planned for urinary incontinence (Meyer et al., 2013). Thus, in the case of low-pressure urethra revealed by UDS the most effective method of the SUI surgery can be selected (Schierlitz et al., 2012). Mean urethral closure pressure has been associated to be an independent risk factor for failure after the transobturator tape procedure (Abdel-Fattah et al., 2010a). UDS may bring out underlying incomplete emptying of the bladder, which may lead to the withdrawal of planned surgery. Detrusor overactivity may be diagnosed more accurately with UDS than based on the patient's symptoms only (Haylen et al., 2014). However, the data regarding the impact of preoperative UDS on the outcome of surgery is not consistent. The outcome of the surgery has shown not to improve after preoperative UDS in patients with uncomplicated SUI (Nager et al., 2012; van Leijsen et al., 2013). There is a substantial variation in the equipment used in UDS. Additionally, the comparison of the results may be difficult because the experience of the person performing the UDS has a significant effect on the reliability of the outcome.

2.7. Mini-invasive urinary incontinence surgery

Based on the integral theory the intra-vaginal slingplasty was introduced in 1996 by Ulmsten and Petros aiming to replace the pubourethral ligaments (Ulmsten and Petros, 1995). This procedure showed poor outcome with unacceptably high complication rates mainly related to the tape

material. The high occurrence of rejection and infections in the intra-vaginal slingplasty tape was associated with a multifilament type III tape (Meschia et al., 2006). This innovation, however, led to further development of the mid-urethral tapes for incontinence surgery along with the introduction of new tape materials.

2.7.1. Tension-free vaginal tape

The most revolutionary innovation based on the integral theory is the tension-free vaginal tape (TVT) procedure introduced by Ulmsten in 1996. In the TVT procedure the polypropylene tape is loosely placed under the mid-urethra. This procedure is presented by Ulmsten et al. in detail (Ulmsten et al., 1996).

The TVT has established its place as the most widely used procedure treating urinary incontinence. Mini-invasive surgery is cost-effective, because it can be performed ambulatory in local anaesthesia with short operative time minimising the risks caused by anaesthesia and invasive surgery (Laudano et al., 2013). By replacing the multifilament tape with monofilament macroporous polypropylene type I tape the tape-related infections and rejections have nearly vanished. Moreover, the intraoperatively removable plastic coating on the tape helps to minimise the risk of infection as well as to adjust the tape during the procedure.

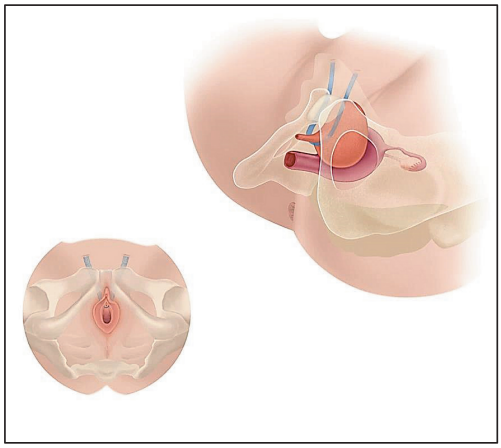


Figure 7. The tension-free vaginal tape (TVT). Reprinted with permission, Ethicon Surgical Care, Sommerville, NJ, USA

The long-term studies have showed good efficacy after the TVT procedure (Table 1). The median for the subjective cure is 84 % after 7 to 17 years of follow-up varying between 57-90 %. Significant improvement is observed in 10-23 % of the patients. The median for objective cure in these studies is 87 % ranging from 69 % to 91 % in 1,127 patients. In all the prospective studies assessing the long-term outcome of TVT preoperative urodynamic studies were performed. The studies were conducted in patients with genuine SUI or in study populations including both SUI and MUI patients. The longest published follow-up concerning TVT is so far 17 years (Nilsson et al., 2013). The initial study population consisted of 90 women with genuine SUI. At the follow-up 46 patients were evaluated objectively and 12 were contacted by telephone. Objective and subjective cure rates were 91 and 87 %, respectively.

Table 1. The long-term follow-up of the tension-free vaginal tape procedure

Author	Study design	Number of patients	Type of incontinence, %	Follow-up, years	Subjective cure, n (%)	Objective cure, n (%)
Liapis et al., 2008	Prospective	61	SUI	7	48 (79) cured 5 (8) improved	49 (80)
Song et al., 2009	Prospective	306	81 SUI 19 MUI	7	212 (69.3)	259 (84.6)
Olsson et al., 2010	Retrospective	104 / 20*	80 SUI 20 MUI	11.5	95 (77) cured 23 (16) improved	87 (84)
Reich et al., 2011	Prospective	108	75 SUI 25 MUI	7	89 (82.4) cured 14 (13) improved	97 (89.8)
Aigmueller et al., 2011	Prospective	117 / 24*	62 SUI 38 MUI	10	81 (57) cured 32 (23) improved	98 (84)
Serati et al., 2012	Prospective	58	SUI	10	52 (89.7)	54 (93.1)
Nilsson et al., 2013	Prospective	46 / 12*	SUI	17	48 (87.2)	42 (91.3)
Svenningsen et al., 2013	Prospective	327 / 156 *	SUI and MUI	10	359 (76.1)	285 (89.9)

*the number of patients evaluated subjectively only

2.7.2. Transobturator techniques

The transobturator techniques were developed to avoid passage through the retropubic space in order to diminish bladder, bowel, and vascular complications. Delorme introduced the outside-in transobturator tape (TOT) procedure in 2001 (Delorme, 2001). It is a mini-invasive, ambulatory procedure where the monofilament polypropylene tape is inserted via skin incisions from the thigh folds through obturator foramen and obturator and puborectalis muscles. This tape was originally coated with silicone in order to diminish retraction of the polypropylene tape. However, silicone coating was later abandoned because of a high exposure rate. The inside-out transobturator procedure, tension-free vaginal tape obturator (TVT-O), was introduced by de Leval in 2003 (de Leval, 2003). In TVT-O the polypropylene tape is led through the obturator foramen from a vaginal incision.

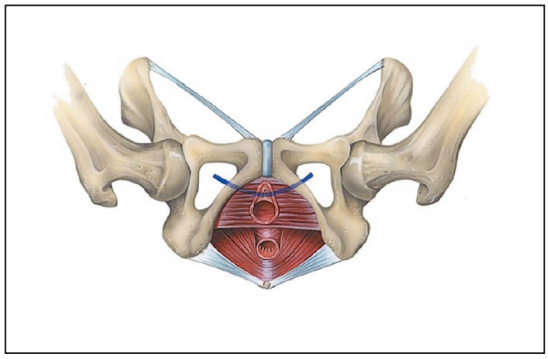


Figure 8. The transobturator tape (TOT). Reprinted with permission, American Medical Systems (AMS), Inc., Minnetonka, USA.

Transobturator procedures are now widely used and the efficacy and safety are well demonstrated in the short- and medium-term follow-up. The results of transobturator tapes after the follow-up between five to seven years are presented in Table 2. After summarizing the studies in Table 2 the median for subjective cure rate is 70 % ranging from 61 to 91.7 % in 905 patients. In addition, the median for objective cure rate is 77 % ranging from 72.9 to 90.8 %. The short- and mid-term outcomes seem to be equal between TOT and TVT-O (Cheung et al., 2013; Latthe et al., 2010). The longest published follow-ups after the TOT outside-in procedure are 5 years (Cañete et al., 2013; Cheung et al., 2013; Yonguc et al., 2014).

Table 2. The subjective and objective outcomes of the trans-obturator tapes after 5 to 7 years of follow-up

Authors	Study design	Number of patients	Type of incontinence, %	Time of follow-up, years	Subjective cure, n (%)	Objective cure, n (%)
Angioli et al., 2010	Prospective TVT-O	37	SUI	5	44 (61)	27 (72.9)
Groutz et al., 2011	Prospective TVT-O	61	66 SUI 44 MUI	5	-	45 (74) cured 5 (8) improved
Cheung et al., 2013	Prospective TOT & TVT-O	104 TOT 82 TVT-O	SUI	5	85 (81.7) TOT 69 (84.1) TVT-O	57 (82.6) TOT 33 (82.5) TVT-O
Canete et al., 2013	Prospective TOT	63	92 SUI 5 MUI	5	49 (78)	50 (79)
Athanasiou et al., 2013	Retrospective TVT-O	124	SUI	7	103 (83.5)	101 (81.5)
Serati et al., 2013	Prospective TVT-O	185	SUI	5	167 (90.3)	168 (90.8)
Laurikainen et al., 2014	Prospective TVT-O	123	SUI	5	121 (91.7)	106 (86.2)
Yonguc et al., 2014	Prospective TOT	126	SUI & MUI	5	83 (65.9)	110 (87)

2.7.3. Retropubic versus transobturator tapes

A Finnish, multicentre randomised clinical trial showed equal efficacy of the retropubic and inside-out transobturator tape after a follow-up of five years (Laurikainen et al., 2014). The objective cure rates were 84.7 % and 86.2 % for the TVT and TVT-O, respectively. In addition, the subjective cure rates were 94.2 % and 91.7 % for the TVT and TVT-O, respectively. The complication rates were equal between the techniques and no tape-related adverse events were detected. Another prospective study comparing the TVT and the inside-out transobturator procedures revealed comparable objective cure rates of 71 % and 72.9 % after TVT and TVT-O, respectively (Angioli et al., 2010). In addition, the complication rates were low and equal between the two techniques used. Equivalent objective and subjective successes after TVT and transobturator tape were reported in a large multicentre study (Richter et al., 2010). Accordingly, similar post-operative subjective satisfaction and improvement of the quality of life were observed. Equivalent objective outcome between the TVT and transobturator procedures has been reported by others (Ballester et al., 2012; Nyyssönen et al., 2013; Porena et al., 2007). A study analysing the cost-effectiveness of TVT vs. transobturator procedures based on 21 randomised controlled trials with a minimum of 12 months of follow-up calculated the cost caused by the differences in efficacy and complications between the two procedures. The authors concluded that the transobturator tape procedures are more cost-effective than the TVT procedure (Seklehner et al., 2014).

2.7.4. Complications after mid-urethral slings

The TVT technique has proved to be safe according to the national register studies in Finland, Austria and France (Agostini et al., 2006; Kuuva and Nilsson, 2002; Tamussino et al., 2001). Minor complication rates in the short-term follow-up are at acceptable level. These complications are mainly perioperative, such as bladder perforations in 3.8-7.3 % in of the patients. Major complications, like damage to vital organs such as blood vessels, bowel or nerves are rare (0-0.08 %) but possibly life-threatening. These may occur as a result of the retropubic needle passage. The most common postoperative complications after TVT are urinary tract infections in 4.1-17 %, retropubic hematoma in 0.3-1.9 %, voiding difficulty in 7.6 % and urinary retention in 2.3-6.6 % of the patients.

The complication rates after the long-term follow-up of TVT have shown to be low. Urinary urgency is the most common long-term consequence and it is considered to significantly lower the quality of life. Tape-related complications, such as exposure into the bladder or through the vaginal mucosa, are rare and in most cases asymptomatic. Only one asymptomatic tape erosion into the vagina was reported after 17 years of follow-up (Nilsson et al., 2013). In addition, others found four exposures of the TVT tape through the vaginal mucosa during the follow-up of 10 years in a study of 327 patients undergone TVT (Svenningsen et al., 2013). The long-term complications after the TVT procedure are presented in Table 3.

The perioperative and short-term complication rates in transobturator techniques are low, 4.7 % in an Austrian registry study with 47 centres and 2,543 operations performed (Tamussino et al., 2007). Vaginal, bladder or urethral perforations occur in 0.1-12.9 % of the patients (Laurikainen et al., 2007; Porena et al., 2007; Tamussino et al., 2001; Wang et al., 2006). Postoperative pain has been reported to occur in 0.5 % of the patients, whereas transient groin pain occurs more often after TVT-O compared to TOT (Abdel-Fattah et al., 2010b; But and Faganelj, 2008; Tamussino et al., 2001). In addition, after a short-term follow-up, voiding disorders are present in 2.7 % of the patients and *de novo* urgency in 3-21 % of the patients undergone transobturator tape procedure (Cañete et al.,

2013; Laurikainen et al., 2007; Porena et al., 2007). Bladder injuries and voiding difficulties have been reported less in the inside-out technique as compared to the outside-in one.

There is a paucity of the long-term follow-up concerning the transobturator tape procedures. During 5-7 years of follow-up adverse events occur rarely. The complications after the transobturator procedures after the follow-up of 5 to 7 years are presented in Table 4.

Table 3. The complications after the tension-free vaginal tape procedure after the follow-up of 7 to 17 years

Complication	Liapis et al.,2008, n(%)	Song et al., 2009, n (%)	Olsson et al., 2010, n (%)	Aigmueller et al., 2011, n (%)	Reich et al., 2011, n (%)	Serati et al., 2012, n (%)	Nilsson et al., 2013, n (%)	Svennigsen et al., 2013, n (%)
***De novo* urgency**	12 (19.6)	2 (0.7)	21 (21.2)	17 (20)	26 (32.1)	11 (18.9)	7 (12%)	15 (14.9)
Vaginal mesh exposure	0 (0)	6 (2)	0 (0)	1 (0.9)	0 (0)	0 (0)	1 (2.2)	1 (0.3)
Voiding difficulties						2 (3.4)		107 (22.8)
Residual volume > 200 ml	0 (0)		4 (3.9)		2 (1.9)		2 (4.3)	0 (0)

Table 4. The complications after the transobturator procedures after the follow-up of 5 to 7 years

Complication	Angioli et al., 2010, n (%)	Groutz et al., 2011, n (%)	Cheung et al., 2014, n (%)	Canete et al., 2013, n (%)	Athanasiou et al., 2013 n (%)	Serati et al., 2013, n (%)	Laurikainen et al., 2014, n (%)
***De novo* urgency**	2 (6.4)	0 (0)	23 (12.4)	11 (17)	6 (7)	45 (24.3)	3 (2.4)
Tape erosion	2 (6.4)	0 (0)	3 (1.8)	10 (27)* 2 (7.7)**	0 (0)	0 (0)	0 (0)
Voiding dysfunction			2 (1.1)				0 (0)
Groin pain	0 (0)		1 (0.5)		0 (0)	0 (0)	

When the complication at issue was not reported in a study the square was left empty in Tables 3 and 4
*Obtape™ **Monarc™

2.8. Pelvic organ prolapse surgery

Kelly and Dumm introduced in 1914 a technique, in which the tissues of the prolapsed anterior vaginal wall and the vesical neck were plicated with interrupted mattress sutures (Kelly and Dumm, 1914). This procedure was originally introduced as an incontinence surgery, but it was gradually adapted as POP surgery because of the dissatisfying results in treating SUI.

In 1938 Ward introduced the anterior colporrhaphy (AC) procedure were the tissues are tightened in the midline of the anterior vaginal wall in order to correct the relaxation of the vaginal wall (Ward, 1938). According to studies with the follow-up of one to three years recurrence rate after AC is reported to be 34.4-65.5 % (Altman et al., 2011; Carey et al., 2009; Nguyen and Burchette, 2008; Nieminen et al., 2010). It is noteworthy that the long-term data concerning the objective outcome of AC is missing. The technique of the posterior colporrhaphy resembles the one in anterior colporrhaphy. Recurrence rate after posterior colporrhaphy is lower than in the anterior repair being 8-21 % after one year of follow-up (Maher et al., 2004a; Paraiso et al., 2006; Singh et al., 2003). In conjunction with colporrhaphies, a vaginal hysterectomy may be performed when required.

Sacrospinous ligament fixation was introduced in Europe in 1981 in order to correct the vaginal vault prolapse (Richter and Albrich, 1981). In this technique the apex of the vagina is attached to sacrospinous ligament with two permanent or slowly absorbable sutures uni- or bilaterally. The outcome of this procedure is well demonstrated in various studies, the objective cure rates have varied between 87-93 % during a follow-up of 5-7 years (Aigmueller et al., 2008; Cruikshank and Muniz, 2003). The typical recurrence after sacrospinous ligament fixationis cystocele, which occurs in 13-14 % of the patients. Severe complications, such as bleeding (0.6-1.4 %), rectum, bladder or ureter injuries (0.6-4.6 %) occur rarely whereas transient buttock pain occurs in 6.5-6.9 % of the patients (Dietz et al., 2008; Hefni and El-Toukhy, 2006; Sze and Karram, 1997).

In sacrocolpopexy (SCP) the vaginal vault, the posterior and commonly also the anterior vaginal wall are attached to the *ligamentum longitudinale* at the level of S2-S3 retroperitoneally with mesh or biological materials using tackers or permanent sutures to restore the apical support. The cure rates of abdominal SCP vary between 76 to 90 % after two years of follow-up (Higgs et al., 2005; Maher et al., 2004b). After two to seven years of follow-up the mesh exposure rate in SCP is reported to be 4-7.1 % (Higgs et al., 2005; Nygaard et al., 2013). Laparoscopic SCP is less invasive than the abdominal leading to a shorter hospital stay and recovery. However, the operative time is longer and the demand of an experienced surgeon is evident (Freeman et al., 2013). The objective cure rate after laparoscopic SCP is comparable to open SCP (Sarlos et al., 2014). Mesh exposure through the vagina or the bladder occurs in 2.9-9.3 % of the patients (Ross and Preston, 2005; Sarlos et al., 2014).

2.8.1. Transvaginal mesh surgery

The rather high risk of recurrence particularly in the anterior vaginal wall led to the development of mesh materials and later on mesh kits to improve the outcome of POP surgery. The anterior and posterior relaxation of the vaginal wall with or without a concomitant vaginal vault prolapse may be corrected with trans-vaginal mesh (TVM). The mesh is placed under the vaginal epithelium and it is left in place tension-freely in order to create a robust layer to replace and strengthen the damaged supportive structures of the pelvic floor. One of the first commercial kits was introduced in 2004 (Fatton et al., 2007). Nowadays there are many commercial kits with slightly different devices and

solutions to implant the mesh. However, polypropylene low-weight mesh is used in all the mesh kits available. In addition, some surgeons shape their own meshes to refrain the use of more expensive commercial kits (Hiltunen et al., 2007).

In studies IV and V the Prolift™ (Ethicon, Sommerville, NJ, USA) mesh kit was used. Prolift™ is a low-weight (42.7 g/m^2), thin (0.42 mm) and high-porosity (64%) with pore size >75µm, one-thread pre-cut polypropylene synthetic mesh retrofitted with arms. In the anterior Prolift™ system the trocar-guided extension arms were passed through the arcus tendineus fascia and obturator foramen and the mesh was placed between the vaginal epithelium and the bladder. In the posterior approach the trocar-guided extension arms were passed through ischiorectal fossa and sacrospinous ligaments and the mesh was placed between the bowel and the vaginal epithelium.

Initially the title used for vaginal mesh surgery was tension-free vaginal mesh (Debodinance et al., 2004; Fatton et al., 2007). Later on, the title transvaginal mesh (TVM) became more frequent, and is now used as a synonym in general (Jacquetin et al., 2013).

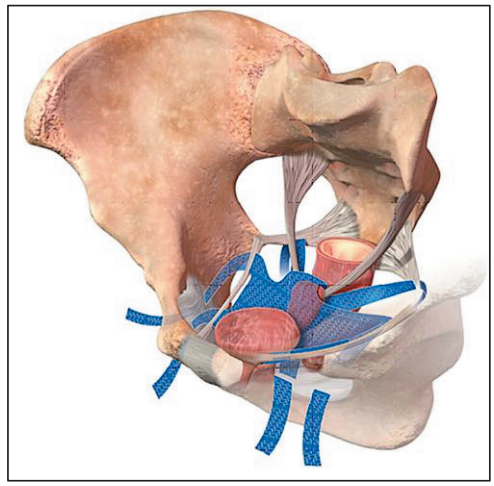


Figure 9. Total Prolift™. Reprinted with permission, Ethicon Surgical Care, Sommerville, NJ, USA

In 2011 the US authority Food and Drug Administration (FDA) gave a warning considering the use of TVM in POP surgery (http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm262435.htm) (FDA July 13, 2011). In the warning the authorities concluded that the complications after TVM associated with mesh are not rare and using TVM introduces the risks not present in traditional non-mesh surgery. In addition, the abdominal mesh surgery produces less mesh complications compared to TVM. Moreover, only the anterior repair with mesh may provide better anatomic results compared to the non-mesh surgery, however, not necessarily resulting in better symptom resolution.

The FDA warning led to the withdrawal of several commercial mesh kits, including the Prolift™ mesh in 2013. Nevertheless, the development of the TVM surgery is continuing. One of the novel mesh kits consists of the polypropylene mesh anchored into the sacrospinous ligament (Stanford et al., 2013). Anatomic success rate was high after one-year follow-up. The need for studies with long-term follow-up regarding TVM surgery is evident. The lack of long-term data is imminent, there are only two studies regarding TVM procedures with the follow-up extending to five years (Jacquetin et al., 2013; Miller et al., 2011).

2.8.2. Objective and subjective outcomes after anterior, posterior and total transvaginal mesh

A Nordic TVM study reported the objective cure rates of 79 % for the anterior repair after one year of follow-up (Elmér et al., 2009). A satisfactory short-term outcome of the anterior repair with the vaginal mesh is confirmed by other investigators (Delroy et al., 2013; Vollebregt et al., 2011). A failure rate of 6.7 % was reported in the anterior compartment after implanting self-tailored mesh (Hiltunen et al., 2007). After one year of follow-up the objective cure rate was 87.7 % in the anterior and 95.9 % in the apical compartment with a mesh anchored in the sacrospinous ligaments (Stanford et al., 2013). The patients' quality of life improved significantly after the anterior TVM according to the studies with short-term follow-up (Delroy et al., 2013; Elmér et al., 2009; Nguyen and Burchette, 2008; Stanford et al., 2013).

The vaginal meshes are less commonly used in the posterior compartment and therefore studies reporting the outcome of the posterior TVM are scarce, the number of patients is small and the anatomical success is not necessarily reported separately for the mesh type used (Milani et al., 2005; Miller et al., 2011; Nair et al., 2011). However, one study with 68 patients undergone the posterior TVM reported an objective cure rate of 82 % and a significant improvement in the quality of life (Elmér et al., 2009). The objective cure rate in a single-incision apical and posterior mesh anchored in sacrospinous ligaments in 139 patients was 92.5 % after the follow-up of one year (Lukban et al., 2012).

The objective cure rate was 81 % for the anterior compartment and 86 % for the posterior compartment after total mesh after one year (Elmér et al., 2009). In prospective studies of three to five years the objective outcome was 84-93 % (Jacquetin et al., 2013; Wang et al., 2013) after the total TVM. The decline in the objective cure rate from 90 % to 84 % was detected after the follow-up of one to five years (Jacquetin et al., 2013).

The longest follow-ups of TVM are stretching into five years. The objective and subjective cure rates of the TVM procedures after three to five years are presented in Table 4. After summarising the studies in Table 4 the median for the objective outcome in 513 patients is 85.3 % ranging from 67 to 93.3 %.

Table 5. The objective and subjective cure rates after the transvaginal mesh procedure

Author	Study design	TVM used	Definition for objective cure	Follow-up time, years	Number of patients	Objective outcome, %	Subjective outcome
de Tayrac et al. 2006	Prospective	Anterior	POP-Q stage ≤ I	1.3 2 3	55	97.9 91.6 89.1	100 97.6 98.2
Nieminen et al. 2010	Prospective	Anterior	POP-Q stage ≤ I No re-intervention	3	104	87	-
Miller et al. 2011	Prospective	Anterior, posterior and total	POP-Q stage ≤ I No re-intervention	1 3 5	83 71 66	88 69 67	Significant reduction in condition-specific questionnaire p<0.001
Benbouzid et al. 2012	Retrospective	Anterior, posterior and total	POP-Q stage ≤ I	4.5	75	85.3	-
Jacquetin et al. 2013	Prospective	Total (one anterior at 5 years follow-up)	The leading edge above the hymen <0 No bulge symptoms or re-intervention	1 3 5	90 85 82	90 88 84	Significant reduction of prolapse symptoms, quality of life improved p<0.001
Gutman et al. 2013	Prospective	Anterior	The leading edge above the hymen <0 No re-intervention	3	51	85	Improvement of the quality of life
Wang et al. 2013	Prospective	Total with hysterectomy	Vaginal vault stage 0 and improvement as stage 1	3	80	93.3	Significant improvement of the quality of life

2.8.3. The outcome of anterior transvaginal mesh compared to other techniques

The objective cure rates are higher after the anterior TVM compared to AC. The definition of the objective cure may vary between the studies; however, most of the authors use the definition of POP-Q stage ≤ I.

Table 6. Objective cure rate after anterior colporrhaphy compared to transvaginal mesh

Author	Objective cure rate Anterior colporrhapy	Objective cure rate Anterior transvaginal mesh	p-value	Follow-up, years
Nguyen et al., 2008	55 %	87 %	p=0.005	2 years
Nieminen et al., 2010	59 %	87 %	p<0.001	3 years
Altman et al., 2011	48 %	82 %	p<0.001	1 year
Menefee et al., 2011	42 %	82 %	p=0.002	2 years
Delroy et al., 2013	56 %	83 %	p=0.018	1 year
Gutman et al., 2013	71 %	85 %	p=0.45	3 years

The reports reveal a significant increase in the quality of life and the symptom resolution after TVM and AC, however, no difference was observed between the groups (Altman et al., 2011; Delroy et al., 2013; Menefee et al., 2011; Nguyen and Burchette, 2008; Nieminen et al., 2010; Vollebregt et al., 2011). The feeling of a vaginal bulge occurs more often after AC than TVM, 38 % vs. 24.6 %, respectively (p=0.008) according to the study comparing the objective and subjective outcomes of 186 patients undergone anterior TVM compared to 182 patients undergone AC (Altman et al., 2011). This result has been confirmed by others (Gutman et al., 2013; Menefee et al., 2011; Nguyen and Burchette, 2008; Nieminen et al., 2010) whereas a similar subjective feeling of bulge was reported in one study (Vollebregt et al., 2011). However, reoperation rate for recurrent POP is similar after TVM and AC after a short-term follow-up (Altman et al., 2011; Menefee et al., 2011; Nguyen and Burchette, 2008; Nieminen et al., 2010; Vollebregt et al., 2011). AC is associated with shorter operative times, lesser occurrence of bladder perforations and less blood loss than the TVM procedure (Altman et al., 2011; Hiltunen et al., 2007; Nguyen and Burchette, 2008; Nieminen et al., 2010).

Comparing the posterior colporrhaphy to self-tailored polyglactin (Vicryl) graft the outcome was similar between the mesh and the non-mesh groups (Sand et al., 2001).

Total TVM had less recurrences (16.9 %) compared to sacrospinous ligament fixation (39.4 %) after one year in a randomised study (Halaska et al., 2012). The subjective outcome and the complication rates were similar in both groups but mesh exposure occurred in 20.8 % of the patients undergone TVM. *De novo* SUI occurred in 35 % and 25 % after total mesh and sacrospinous ligament fixation, respectively. In another study a similar anatomic outcome and impact on the quality of life were observed between the two techniques, the mesh exposure rate being 35.7 %, however (Lopes et al., 2010).

Total TVM has been compared to laparoscopic SCP in a randomised study following patients for two years (Maher et al., 2011). Laparoscopic SCP had an objective cure rate of 77 % compared to 43 % in the TVM group when cure was defined as POP-Q ≤ 1 at any site of the vagina. One patient had symptomatic prolapse (2 %) in the LSC group and 4 (7 %) in the TVM group without statistical

significance. The laparoscopic SCP surgery took twice as long as TVM but was associated with shorter hospitalisation and a faster return to daily activities. The subjective outcome was significantly better among patients who underwent laparoscopic SCP.

2.8.4. Complications after transvaginal mesh procedures

Perioperative and short-term postoperative complications after TVM are bladder injuries in 0-3.2 %, vaginal hematoma in 0.8 %, urinary tract infections in 4.8-20 %, groin/buttock pain in 2.5 % and urinary retention in 2.5-13 % of the patients (Delroy et al., 2013; Elmér et al., 2009; Hiltunen et al., 2007). *De novo* SUI is observed in 3.9-23 % of the patients after the follow-up of one to 4.5 years (Benbouzid et al., 2012; Hiltunen et al., 2007; Nair et al., 2011; Nieminen et al., 2010; Stanford et al., 2013) occurring significantly more often after TVM compared to AC (Altman et al., 2011; Nieminen et al., 2010).

De novo dyspareunia rates have been reported to be 2.5-17 % after TVM (Benbouzid et al., 2012; de Tayrac et al., 2006; Gutman et al., 2013; Jacquetin et al., 2013; Miller et al., 2011). A study assessing symptom resolution and sexual function after the anterior wall repair with or without mesh did not report any changes in dyspareunia rates between the pre- and postoperative situation (Nieminen et al., 2008). In addition, others did not find any difference in scores evaluating the sexual function between the two groups (Altman et al., 2011; Nguyen and Burchette, 2008).

Mesh exposure through the vaginal mucosa is reported to occur in 5-17.3 % of the patients after follow-up of one to two years (Delroy et al., 2013; Elmér et al., 2009; Hiltunen et al., 2007; Nair et al., 2011; Nieminen et al., 2008; Stanford et al., 2013). The complications after three to five years after TVM are presented in Table 7.

Failure rates and reoperations due to pelvic organ prolapse after the transvaginal mesh procedure after the follow-up of three to five years are presented in Table 8.

Table 7. The long-term complications and surgical correction of the mesh after the follow-up of three to five years after transvaginal mesh

Complication	de Tayrac et al., 2006	Nieminen et al., 2010	Miller et al., 2011	Benbouzid et al., 2012	Jacquetin et al., 2013	Gutman et al., 2013	Wang et al., 2013
Follow-up, years	3	3	5	4.5	5	3	3
Exposure n, (%) • **During** • **At last follow-up**	5 (9.1) 0 (0)	20 (19) 5 (5)*	16 (19) 4 (6)*	4 (5.3) 0 (0)	14 (16) 7 (8.5)*	5 (20) 1 (4)*	5 (6.3) 0 (0)
Surgical correction of exposure, n / all exposures (%)	5/5 (100)	14/20 (70)	9/16 (56)	2/4 (50)	8/14 (57)	3/5 (60)	1/5 (20)
Unprovoked vaginal pain, n (%) **Provoked pain, n (%)**	3 (5.5)				1 (1.2) 5 (5.6)		
Voiding difficulties, n (%)	7 (12.7)		1 (1.5)				

* Persistent exposures

When the complication at issue was not reported in a study the square was left empty

Table 8. Failure rates and reoperations due to pelvic organ prolapse after the transvaginal mesh procedure after the follow-up of three to five years.

	Recurrence in treated compartment, n (%)	**Surgical correction, n (%)**	**Recurrence in adjacent compartment, n (%)**	**Surgical correction, n (%)**
Nieminen et al., 2010	14 (13)	0 (0)	16 (15)	6 (6)
De Tayrac et al., 2006	6 (11)	0 (0)	10 (18)	0 (0)
Miller et al., 2011	15 (23)	2 (3)	7 (11)	3 (4.5)
Benbouzid et al., 2012	5 (6.7)	0 (0)	6 (8)	0 (0)
Jacquetin et al., 2013*	13 (16)	4 (5)		
Wang et al., 2013*	5 (6.3)	0 (0)		

Failure was defined as POP-Q stage ≥ 2 or as the leading edge below the hymen >0
The square was left empty if the issue was not reported in a study
*total TVM

3. AIMS OF THE STUDY

To investigate and compare the differences of connective tissue, e.g., elastin and collagen in the vaginal wall of patients with and without pelvic organ prolapse.

To evaluate the long-term outcome of the tension-free vaginal tape (TVT) procedure for stress urinary incontinence among female patients who have been operated on without preoperative urodynamic studies.

To study the long-term outcome of the transobturator tape (TOT) procedure for female stress urinary incontinence.

To explore the initial experiences and short-term success of pelvic organ prolapse surgery with polypropylene mesh.

To evaluate the long-term outcome and complications of pelvic organ prolapse surgery with polypropylene mesh.

4. MATERIALS AND METHODS

4.1. Patient characteristics and study design

4.1.1. Study I

The Study I was carried out between October 2009 and June 2010 in Turku University Hospital, Department of Obstetrics and Gynaecology. The study population consists of patients scheduled for vaginal surgery due to POP (n=39) and controls for hysterectomy for benign indications other than POP (n=39). The grade of POP was assessed on the day of the surgery by POP-Q system (Bump et al., 1996).

Tissue samples were obtained with cold instruments during the surgery from the anterior wall of the vagina in the midline close to cervix or apex avoiding clear scarred tissue in the case of previous vaginal surgery. Samples were obtained considering the adequate thickness, which includes all four histologic layers of the vaginal wall.

Samples were immediately sent to a pathologist and dissected into serial sections for van Gieson (VG), Movat's Pentachrome (Movat, 1955) and immunostaining. The tissue samples were analysed by a gynaecologist and a pathologist. Examinations were carried out blinded as to the other investigator and to the POP status. In case of discrepancy the investigators evaluated the samples together to gain consensus.

The VG-stained samples were first examined in order to ensure that all the four layers of the vaginal wall were present in the samples. The visualisation of elastin fibres in the tissue samples was analysed using Movat's Pentachrome staining. After deparaffinisation and hydration of the sections, staining was performed using a commercially available staining kit (F-384, Rowley Biochemical Inc., Danvers, MA, United States), exposing sectioned tissue samples to Alcian blue, Resorcin-Fuchsin, Weigert's hematoxylin, Woodstain-Scarlet and safran solutions. Visualisation of elastin in the tissue sections was morphometrically estimated according to a three-grade visual scale (1-3) designed by the investigators. Grade 1 represented minimal elastin and grade 3 represented an abundance of elastin. Visualisation of elastin was reported separately in sub-epithelium and in the total sample consisting all the four layers of the vaginal wall.

The immunohistochemistry was performed in order to observe type I, III and V collagens in the tissue samples. Immunohistochemistry was performed on the sections adjacent to those used for VG and Movat-staining. The binding of the primary antibody was detected using the BrightVision plus poly-HRP-anti Ms/Rb/Rt IgG detection system (ImmunoLogic, AD Duiven, Netherlands). For the detection of type I, III and V collagens, monoclonal antibodies clone COL-1 dilution 1:2000 (Sigma-Aldrich, St. Louis, MO, USA), clone FH-7A dilution 1:4000 (Sigma-Aldrich) and clone V-3C9 dilution 1:3000 (Merck Millipore, Billerica, MA, USA), were used. Antibodies were diluted in Dako Antibody Diluent (Dako, Glostrup, Denmark). Epitope retrieval was performed in a microwave oven in Tris-EDTA-buffer (pH 9), after which antibody binding to antigen (1 h at room temperature) and binding of HRP-labelled secondary antibody were performed. The detection with diaminobenzidine was performed using an automatic staining machine (LabVision Corporation, Fremont, CA, United States).

The clinical details of the patients were gathered from the hospital records. Postmenopause was defined as absence of menstruation for at least one year.

4.1.2. Studies II and III

Study II is a follow-up study consisting of 191 patients operated on with the TVT procedure between January 1998 and May 2000 at the Department of Obstetrics and Gynaecology in the Turku City Hospital, Turku, Finland. The TVT procedure was performed as described previously by Ulmsten (Ulmsten et al., 1996). The commercial TVT kit was used in every procedure (TVT™ Gynecare, Ethicon, Somerville, NJ, USA). Cystoscopy was performed after each retropubic passage of the needle. The perioperative supine stress test with 300 ml bladder filling was performed to adjust the tape.

Study III is a clinical follow-up study involving 191 patients operated on at Turku University Hospital between May 2003 and December 2004 using the outside-in transobturator tape (TOT) procedure. The TOT procedure was performed as described by Delorme et al. in 2001 (Delorme, 2001). The commercial outside-in TOT kit was used in every procedure (Monarc™, American Medical Systems (AMS), Inc., Minnetonka, USA). Routine cystoscopies or supine stress tests were not performed.

The urinary incontinence was defined as a history of involuntary leakage during stress and with supine stress test along with a physical examination.

Patient characteristics in Studies II and III are presented in Table 9.

Table 9. Patient characteristics in Studies II and III original study populations

	Study II n=191	**Study III n=191**
Age, median (range)	60 (32–84)	59 (31–86)
BMI, median (range)	27 (19–39)	27 (19–50)
Stress incontinence, n (%)	127 (66)	127 (66)
Mixed incontinence	64 (34)	64 (34)
Chronic illnesses, n*	74	100
Previous incontinence surgery, n (%)	39 (20)	32 (17)
Concomitant surgery, n (%)	34 (18)	85 (45)

*One patient may have had one or more chronic illnesses

After the median of 10.5 and 6.5 years of follow-up in Studies II and III, respectively, hospital records of all the patients were reviewed. Postal questionnaires were sent to patients in order to evaluate the subjective outcome. An invitation for a follow-up visit free of charge at the Turku University Hospital, Outpatient Clinic of Gynaecology was sent to patients in order to assess the objective outcome. A gynaecological examination along with a supine stress test with an estimated bladder volume of 250 to 300 ml was performed at the follow-up visit.

In Study II the subjective outcome was defined as scores of 0 to 7 in IIQ-7 and the expression of satisfaction at the telephone interview. In Study III the subjective outcome was defined with the

questions: “Are you satisfied with the operation?” and “Would you recommend this operation to your friends?”, both included in the self-tailored questionnaire.

The objective cure was defined as a negative stress test and no repeat operation because of SUI during the follow-up.

In Study II urgency or UUI was diagnosed if the patient had marked moderate or severe frequency or urgency (scores 2 or 3) in questions one and two of the UDI-6 questionnaire and DIS score was > 7. In Study III the definition of urgency or UUI was a score of > 7 in the DIS questionnaire.

4.1.3. Study IV

Study IV is a clinical follow-up study covering the first 100 patients operated on in the Turku University Hospital between June 2005 and April 2007 using the anterior, posterior or total TVM. The indication for using mesh was a recurrent vaginal prolapse or a large primary prolapse and/or apical prolapse. The surgeon made the decision concerning the surgical technique and possible concomitant procedures performed.

The procedure was performed as described by Debodinance et al. (Debodinance et al., 2004) using transvaginal mesh kit (Prolift™, Ethicon, Sommerville, NJ, USA). The mesh was placed under the fibromuscular layer of the vaginal wall. Vaginal epithelium was closed with continuous or separate absorbable stitches. Vaginal packing and urinary catheter were used routinely and they were removed in the next morning. All patients were advised to use vaginal oestrogen postoperatively.

The peri- and postoperative data was collected from the hospital records up to the postoperative visit two to three months after the operation. After the mean of one year a questionnaire designed by the investigators with a detailed list of symptoms was sent to the patients to assess the subjective cure and satisfaction for the procedure.

4.1.4. Study V

Study V consists of the first 200 TVM procedures performed in 195 patients operated on between June 2005 and March 2009 in Turku University Hospital using TVM. The data concerning the first 100 patients is published in Study IV. Study V consists of the population from study IV with the addition of the following 95 patients operated on with polypropylene mesh. The decision concerning the surgical technique and possible concomitant procedures performed is identical between Studies IV and V.

The medical history of the patients and the postoperative data were collected from the hospital records. After a median of seven years validated questionnaires were sent to patients in order to assess the subjective outcome. The subjective satisfaction on the procedure was assessed with the question: “Are you satisfied with the procedure?” included in one of the questionnaires. An invitation for a follow-up visit free of charge at the Turku University Hospital, Outpatient Clinic of Gynaecology, was sent to the patients. The objective outcome was evaluated at the follow-up visit in a gynaecological examination performed by one of the four investigating gynaecologists. An evaluation of the current anatomy was performed with POP-Q system (Bump et al., 1996). Mesh-related complications were reported using the Prosthesis/Graft Complication Classification Code designed by the International Continence Society and the International Urogynecological Association (ICS/IUGA) (Haylen et al., 2011). The anatomical cure was defined using two different definitions: as a POP-Q stage ≤ 1 and as vaginal wall prolapse at or above the hymen (points Ba

or Bp ≤ than 0 cm) or vaginal apex not descending below the upper third of the vagina (point C above -2/3 of the total vaginal length) (Nygaard et al., 2013).

4.2. Validated questionnaires

The Urogenital Distress Inventory-6 and Incontinence Impact Questionnaire-7 Studies II and III

The Urogenital Distress Inventory (UDI) and the Incontinence Impact Questionnaire (IIQ) were developed based on patient interviews, clinician's opinions and literature reviews along with the testing of the pilot questionnaires (Shumaker et al., 1994). These detailed questionnaires include relatively many questions, 30 in IIQ and 19 in UDI. To make questionnaires easier to use and to enhance the patient's readiness to collaborate, the questionnaires were shortened (Uebersax et al., 1995). The short forms UDI-6 and IIQ-7 are widely used in the studies regarding pelvic floor disorders. UDI-6 consists of six questions concerning urinary frequency, urinary urgency, SUI and voiding difficulties. IIQ-7 is a questionnaire with seven questions assessing the bother caused by UI symptoms consisting of five questions covering the impact of symptoms in activities and two covering the patient's subjective emotions. If a patient did not answer >2 items on the IIQ-7 or UDI-6 questionnaires a total score was not calculated.

Urinary Incontinence Severity Score Studies II, III and V

Urinary Incontinence Severity Score (UISS) was designed by the Finnish Gynaecological Society's urogynaecological working group in 1992 (Mäkinen et al., 1992) and it has proven to be a valid and reproducible questionnaire (Stach-Lempinen et al., 2001). UISS consists of ten questions covering the effect of the symptoms of UI in everyday life with the scores of minimum 0 and maximum 20. When the total score reaches 50 % of the scores, the symptoms are considered to be significant, and intervention is indicated.

Detrusor Instability Score Studies II, III and V

Detrusor Instability Score (DIS) (Kauppila et al., 1982) was introduced in 1982 and is now used in Finland in everyday clinical practice together with UISS as an instrument for pre- and postoperative evaluation of UI. DIS is a questionnaire with ten questions concerning the symptoms of the lower urinary tract. Each question has scores 0, 1 or 2, and the maximum score in total is 20. The score seven or less indicates SUI and scores higher than seven refer to more urgency-related symptoms.

EuroQoL-5D Studies II, III and V

EuroQoL-5D (EQ-5D) (Group, 1990) is a standardised validated non-disease-specific questionnaire assessing the patient's global health. This questionnaire consists of five questions concerning mobility, self-care, usual activities, pain or discomfort and anxiety or depression. Answer options are no problems, moderate problems or extreme problems. EQ-5D VAS is a thermometer-like scale, which evaluates the state of health at a moment of filling out the questionnaires.

The Visual Analogue Scale Studies II, III and V

The Visual Analogue Scale (VAS) is a line from 0 to 10 or 100, where the patient may draw a mark when describing the symptom severity. Zero reflects no symptoms and 10/100 remarkable symptoms (Stach-Lempinen et al., 2001). VAS is a valid and repeatable tool when assessing the bother regarding pelvic floor disorders (Ulrich et al., 2014).

Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire short form Study V

Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-31) was developed to evaluate sexual function in patients with pelvic floor disorders (Rogers et al., 2001). PISQ-31 was designed after a review of literature and of non-specific validated instruments. It consists of 31 questions concerning sexual activity and possible disturbing symptoms of urinary incontinence and POP affecting the sexual life. It was later on shortened to include 12 questions to make it more functional in clinical practice and in research (Rogers et al., 2003). Each response has five options and scaling from 'never' = 0 to 'always' = 4. The short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) is widely used for research purposes.

Pelvic Organ Prolapse Distress Inventory Study V

Pelvic Organ Prolapse Distress Inventory (POPDI-6) is one of the scales used in Pelvic Floor Distress Inventory (PFDI-20). PFDI-20 is a condition-specific validated questionnaire covering the bother and distress caused by pelvic floor symptoms (Barber et al., 2005). POPDI-6 consists of six questions concerning the bother caused by POP. Every question has four options from 'not at all' = 1 to 'quite a bit' = 4.

Colorectal-Anal Questionnaires

Colorectal-anal symptoms were evaluated using a questionnaire, which is used in everyday practice in the Outpatient Clinic of Gynaecology of Turku University Hospital. This questionnaire consists of detailed questions concerning symptom severity of anal incontinence and constipation (Khaikin and Wexner, 2006). Wexner score is used for evaluating the symptom severity of anal incontinence. Each question has scores from 0 to 4, the highest score being 20. The score ≥ 9 indicates significant impact on the quality of life.

Self-Tailored Questionnaires Study III and IV

Self-tailored questionnaires were used to assess the patient's subjective outcome in Studies III and IV. The self-tailored questionnaire used in Study III was applied because it was earlier used in the same study population in short-term evaluation (Joutsiniemi et al., 2009). At the time of the study IV there were no validated symptom-specific questionnaires concerning gynaecological prolapses available in Finnish.

The questionnaires used in Studies II to V are presented in Table 10.

Table 10. Questionnaires used in Studies II to V. The clarification of the abbreviations in the Table 10; see Abbreviations and Chapter 4.2.

	Study II	Study III	Study IV	Study V
UISS	X	X		X
DIS	X	X		X
UDI-6	X	X		
IIQ-7	X	X		
EQ-5D	X	X		X
EQ-5D VAS	X	X		X
PISQ-12				X
POPDI-6				X
Wexner score				X
Self-tailored symptom-specific questionnaire		X	X	

4.3. Statistics

Data was summarised using percentages or mean values and standard deviations (SD). Comparisons between the two categorical variables were analysed using cross-tabulations and the association between the variables was tested using a chi-square test or Fisher's exact test in case the table frequencies were small. The mean differences between the groups in the continuous variables were compared using an independent samples t-test. Associations between the continuous predictive variables and the nominal response variables were tested using logistic regression for dichotomous response variables, multinomial logistic regression for multinomial response variables, and a cumulative logit model for ordinal response variables. In all statistical tests, a p-value <0.05 was considered to be statistically significant. All statistical analyses were performed using statistical software SAS (version 8.2, 9.2 and 9.3).

All the studies were approved by the Ethics Committee of the Hospital District of Southwest Finland.

5. RESULTS

5.1. Study I

Seventy-eight patients were enrolled in the Study I, 39 patients with POP and 39 as controls. Patients with POP were significantly older (p<0.001), more often postmenopausal (p<0.001) and they more often used vaginal oestrogen (p<0.001). Twenty-one (53.8 %) patients were operated on because of POP-Q stage 2 and 18 (46.2 %) because of stage 3.

BMI, history of deliveries or previous prolapse surgery had no influence on the presence of elastin in tissue samples. The visualisation of grade 3 elastin in tissue samples in patients with and without POP is presented in Table 11.

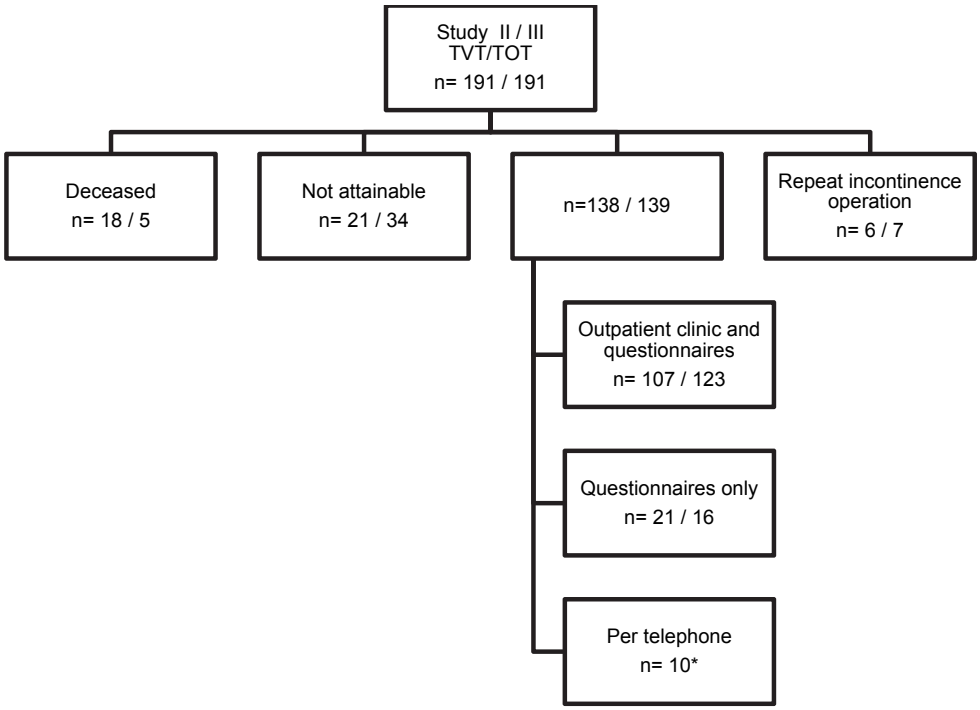
Table 11. Visualisation of grade 3 elastin in tissue samples in patients with and without POP in Study I

Grade 3 elastin	In sub-epithelium	In entire tissue sample
POP **Control**	22 (56.4 %) 1 (2.6 %); p<0.001	19 (48.7 %) 5 (12.8 %); p<0.001
Premenopausal **Postmenopausal**	2 (5.6 %) 21 (50 %); p<0.001	5 (13.8 %) 19 (45.2 %); p<0.01
Vaginal oestrogen **Without vaginal oestrogen**	17 (51.5 %) 6 (13.6 %); p<0.001	17 (51.5 %) 7 (15.9 %); p<0.001

The tendency of more intense immunostaining of type III and V collagens was observed in patients with POP. Type I collagen formed a more prominent layer under the stratified squamous epithelium in controls compared to patients with POP. Patients with POP had a tendency to have a more distinguishable smooth muscle layer than controls.

5.2. Studies II and III

The study populations in Studies II and III are presented in Figure 10.



* in Study II

Figure 10. Study population in Studies II and III

Patient characteristics in Studies II and III are presented in Table 12.

Table 12. Patient characteristics in Studies II and III

	Study II n =128*	**Study III n = 139**
Age, mean, SD	68 ±10	65 ±10
BMI kg/m², mean, SD	27 ±4.4	28 ±4.8
Parity, mean, SD	2.3 ±1.1	1.7 ±1.3
Oestrogen, n (%)**	77 (69)	78 (56)
Chronic illnesses, n (%)	100***	74 (53)
Previous incontinence operations, n (%)	22 (16)	19 (14)
Type on incontinence preoperatively, n (%) • **SUI** • **MUI**	 101 (73) 37 (27)	 90 (65) 49 (35)
Concomitant procedures, n (%)	27 (21)	51 (37)
Incontinence surgery after the TVT or TOT operation, n	6 (4.7)	7 (5)

*The 10 patients contacted by telephone are not included in this cohort.
**Vaginal and/or systemic oestrogen. ***One patient may have had one or more chronic illnesses.

In Studies II and III the patients with MUI preoperatively had significantly higher scores in the condition-specific questionnaires (UISS, DIS, IIQ-7, UDI-6 and VAS) compared to patients

operated on because of genuine SUI indicating more bothersome urinary symptoms (p<0.001 in studies II and III). Moreover, the quality of life and health was lower in the patients with preoperative MUI (p<0.05 and p< 0.01 in Studies II and III, respectively).

In Study III the patients with BMI >30 kg/m² had significantly more bothersome urinary symptoms according to condition-specific questionnaires compared to patients with BMI ≤ 30 kg/m² (p-values varying between p<0.5 and p<0.001 in the questionnaires). The scores in the questionnaires assessing the quality of life and health were significantly lower in patients with BMI >30 kg/m² compared to patients with BMI ≤ 30 kg/m² (EQ-5D and EQ-5D VAS p<0.05 and p<0.001, respectively).

The results were comparable in all questionnaires in Studies II and III between the patients operated on because of recurrent SUI compared to patients operated on with primary SUI. The only exception was DIS in Study III, with scores indicating significantly more urgency or UUI (p< 0.01) in patients with recurrent SUI compared to patients with primary SUI.

Concomitant surgery, procedure due to recurrent SUI, and BMI >30 kg/m² did not have an effect on the objective cure rate in study III. Subjective satisfaction and objective outcome in Studies II and III are presented in Table 13.

Table 13. Subjective satisfaction and objective outcome in Studies II and III

	Study II	**Study III**
Subjective satisfaction, % • **BMI ≤ 30** • **BMI > 30** • **SUI preoperatively, %** • **MUI preoperatively, %**	78	83 85 84 92 76 (p<0.001)
Objective outcome, %	90	89

Seven out of ten patients contacted by telephone in Study II expressed themselves to be continent, whereas two complained symptoms of SUI and one patient those of UUI.

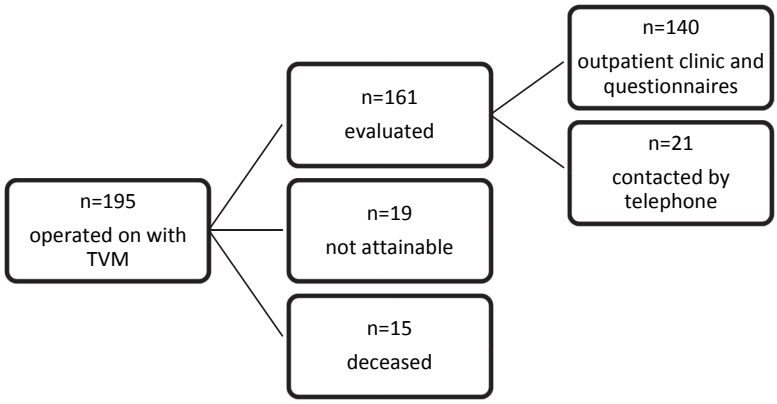
A total of 18 (14 %) and 53 (39 %) of the evaluated patients reported urgency or UUI in Studies II and III, respectively. Failures and tape-related complications are presented in Table 14.

Table 14. Failures and tape-related complications after the mid-urethral sling procedures in Studies II and III

	Study II	**Study III**
Reoperations due to urinary incontinence, n (%)	6 (4.7)	7 (5)
Positive stress test, n (%)	6 (5.6)	12 (8.6)
Tape-related complications:		
Cutting of the tape due to retention, n (%)	2 (1.6)	1 (0.7)
Resection of the tape due to exposure, n (%)		
• **Vagina**	0 (0)	1 (0.7)
• **Bladder**	1 (0.8)	0 (0)

5.3. Studies IV and V

In Study IV the study population consisted of the first 100 patients operated on using TVM in Turku University Hospital. The study population in Study V consisted of the 100 patients from Study IV with the addition of the following 95 patients operated on with TVM. The study population in Study V is presented in Figure 11.



Adopted from manuscript of Heinonen et al.: Long-term outcome after transvaginal mesh repair of pelvic organ prolapse

Figure 11. Study population in Study V

Patient characteristics in Studies IV and V are presented in Table 15

Table 15. Patient characteristics in Studies IV and V in patients operated on with TVM

	Study IV n= 100	**Study V n= 161**
Age, mean SD	65 ±10	72 ±9.4
BMI kg/m², mean SD	27 ±3.7	27 ±4.3
Parity, mean SD	2.6 ±1.3	2.7 ±1.3
Previous POP surgery, n (%)*	47 (47)	74 (46)
• **Colporrhaphy**	39	64
• **Hysterectomy**	29	50
• **Sacrospinous fixation**	9	14
• **Sacrocolpopexy**		1
Patients with 2 or more previous POP procedures, n (%)	43 (43)	46 (28.6)
Anti-incontinence operations, n (%)	16 (16)	28 (17.4)
Type of mesh used, n (%)		
• **Anterior**	48 (48)	74 (46)
• **Posterior**	45 (45)	73 (45)
• **Combined anterior and posterior**	2 (2)	4 (2.5)
• **Total**	5 (5)	10 (6.2)

*One patient may have had one or more previous procedures performed

Table 16 presents the distribution of the mesh types and intra- and postoperative complications in Study IV.

Table 16. Intra- and postoperative characteristics and complications in Study IV

	Study IV n=100
Operation time, median (range)	72 min (27–160)
• Anterior mesh	88 min (27–160)
• Posterior mesh	60 min (30–83)
• Total mesh	110 min (72–160)
• Anterior and posterior mesh	113 min (110–125)
Blood loss, median (range)	100 ml (10–1100)
• Anterior mesh	180 ml (30–110)
• Posterior mesh	45 ml (10–500)
• Total mesh	150 ml (50–550)
• Anterior and posterior mesh	350 ml (250–450)
Hospital stay, median (range)	3 days (0–12)
Complication, n*	
• **Bleeding > 1000 ml**	2
• **Transient urinary retention**	5
• **Hematoma**	2
• **Mesh exposure**	14
• **Patients with postoperative antibiotic treatment**	28
• ***De novo* SUI**	20

*One patient may have had more than one complication

In Study IV 89 patients responded to a self-tailored questionnaire after the mean of one year of follow-up. Altogether 60 % of the patients reported all preoperative symptoms cured.

The scores of the validated questionnaires assessing urinary or anal incontinence, constipation, PISQ-12 and EQ-5D are presented in Table 17. Dyspareunia was reported never in 20 (51.3 %), seldom or sometimes in 16 and usually in 5 out of 39 sexually active women. Sexual intercourse was never avoided in 32 (82 %), and sometimes or seldom in seven women due to bulge in the vagina.

Table 17. The scores of the questionnaires assessing urinary incontinence, general quality of life and health, Wexner score (anal incontinence), constipation and PISQ-12. Adapted from the manuscript of Heinonen et al.: Long-Term Outcome after Transvaginal Mesh Repair of Pelvic Organ Prolapse: a main research article

UISS	15 (0-28)	0-100
DIS	5 (0-8)	0-20
VAS for urinary incontinence	2 (0-4.5)	0-10
EQ-5D index	0.68 (0.33-1)	0-1
EQ-5D VAS*	7.5 (3-10)	0-10
Wexner score	0.00 (0-20)	0-20
VAS for anal incontinence	0.5 (0-9.5)	0-10
VAS for constipation	2 (0-9.5)	0-10
PISQ-12	12 (5-29)	0-48

In Study V concomitant surgery was performed in 58 (36 %) patients. Altogether 90.7 % of the patients had the leading descending point at or above the hymen. The subjective satisfaction and objective outcomes and reoperations in Studies IV and V are presented in Table 18.

Table 18. The subjective and objective outcomes and reoperations in Studies IV and V

Outcomes and reoperations	**Study IV**	**Study V**
Subjective satisfaction, % • **Patients with complication** • **Patients undergone reoperation due to POP**	70.8	80.1 80.5 78
Objective outcome, definition • **POP-Q stage ≤1** • **Leading point at or above hymen and apex above -2/3 of total vaginal length**		 56.4 % 69.3 %
Reoperations, n (%) • **Due to POP in untreated compartment** • **Due to POP in treated compartment** **Mid-urethral tape** **Resection due to mesh exposure**	 12 (12) 16 (16) 9 (9)	 18 (11.2) 8 (5) 25 (15.5) 18 (11.1)

Altogether 45 (32 %) patients experienced mesh complications in Study V. Mesh exposure was detected in 32 (22.5 %) patients. Mesh exposures in studies IV and V are presented in Table 19.

Table 19. Mesh exposures after TVM surgery in studies IV and V

	Study IV	**Study V**
		Number of exposures in 32 patients
Mesh exposure through vaginal mucosa, n • **Asymptomatic** • **Provoked pain in gyn. examination** • **Dyspareunia** • **Unspecified symptoms**	14	36* 24 6 2 4
Size of exposures		25 ≤ 1 cm 11 > 1cm
Site of exposure, n • **Area of suture line** • **Away from suture line**		 29 7
Persistent, n (%) **Late onset, n (%)**		10 (27.8) 26 (72.2)

* Four patients had concurrent mesh exposure in two sites; three patients in total mesh and one patient in two separate meshes

6. DISCUSSION

Pelvic floor disorders significantly lower the quality of life of women affected. Understanding the pathophysiology of these common disorders may guide the development of pelvic floor surgery. Studying the changes in the fibroelastic composition of the vaginal wall connective tissue clarifies the unclear process leading to the development of POP and SUI. The main goal in pelvic floor surgery is the resolution of symptoms, improvement of the quality of life and subjective satisfaction of women. In order to assess the efficacy and safety of the surgical techniques the evaluation of subjective outcome and complications is essential. The durability of the treatment needs to be observed in the long-term because of the possible deteriorating of the outcome. In addition, complications may continue to occur over time.

6.1. Changes in elastin and collagens in vaginal wall

In Study I more elastin was observed in the tissue samples from the vaginal wall of the patients with POP as compared to that of the controls. The changes in the connective tissue of patients with POP may be the result of an active and forceful repair of the injured tissues rather than the cause (Chen and Yeh, 2011). High elastin content in the prolapsed tissue may be the result from the degradation and remodelling of the elastin fibres after tissue trauma and chronic load caused by prolapse. A higher amount of elastin and type III collagen have been observed in prolapsed tissue as compared to non-prolapsed tissue of the same patients (Kerkhof et al., 2014). However, the data concerning elastin is inconclusive. Another study showed a significant decrease in the elastin density in the most distal portion of the vaginal wall of women suffering from POP (de Landsheere et al., 2014) . Metabolically repaired elastin may be frail and malformed thus leading to increasing risk for POP in the future (Yamamoto et al., 1997).

In the present study type I collagen stained more intensively under the stratified squamous epithelium in the control samples compared to the samples obtained from the patients with POP. Moreover, a slight increase in the amount of types III and V collagen in the patients with POP was observed. Type I collagen fibres are longer and thicker than the fibres in type III and V collagens giving the highest tensile strength. An increase of type III and V collagens may impair mechanical properties of tissues because the smaller fibre size of these collagens gives tissue more elasticity and flexibility. Only minor changes in the ratios of different collagens may reduce the mechanical properties of the connective tissue (Birk et al., 1990). The decreasing I/III ratio is more common among the patients with than without POP (Yucel et al., 2013). The amount of type III and V collagens is observed to increase in the vaginal wall in patients with POP compared to controls (Moalli et al., 2005). In concordance, other studies have observed increased type III collagen expression in the vaginal wall and uterosacral ligaments in patients with POP (Gabriel et al., 2005; Mosier et al., 2010). On the contrary, a diminished type III collagen content and a lower protein expression of type III collagen in the vaginal wall have been reported (Lin et al., 2007; Zhou et al., 2012). Decreasing type III collagen content was connected to more rigid tissues in the patients with POP (Zhou et al., 2012).

In the present study it was not possible to present pairs matched by age and menopausal status owing to the challenges in the recruitment of postmenopausal women undergoing gynaecological surgery due to other benign reasons than POP. However, in a well-designed study the most pronounced differences in collagen content in the vaginal wall biopsies were between the patients

with POP and the controls, independent of menopausal status (Moalli et al., 2005). Others found type III collagen increase to be associated to the presence of POP but not to age or parity (Gabriel et al., 2005). Menopause in the absence of hormone therapy may lead to a decrease in the amount of type I collagen in the supportive structures of the pelvic floor possibly causing weakening of the tissues (Moalli et al., 2004).

6.2. Outcomes of mid-urethral slings

In the present study the overall subjective cure rates are slightly inferior to other long-term studies being 78 % and 83 % after TVT and TOT, respectively. The subjective outcome of TVT was 87 % after the follow-up of 17 years in patients with genuine SUI without previous incontinence surgery when the subjective cure is defined as cured or significantly improved (Nilsson et al., 2013). In addition, after five years of follow-up 91.7 % subjective cure was reported after transobturator tape procedures in an uniform patient population (Laurikainen et al., 2014). However, in Studies II and III the study populations were heterogenic as one third of the patients had MUI preoperatively and about one fourth of the patients were operated on because of recurrent SUI. In addition, a significant difference in the satisfaction of the surgery after TOT between SUI and MUI patients, 92 % and 76 % ($p<0.001$), respectively, was observed. The patients with MUI experience more bothersome urinary symptoms compared to the patients with genuine SUI. This may lead to dissatisfaction with the procedure even if SUI is cured. Overall subjective cure rates in study II were comparable to other long-term studies of TVT where the study populations included 19-38 % patients with MUI (Aigmueller et al., 2011; Olsson et al., 2010; Reich et al., 2011; Song et al., 2009). In addition, a similar subjective cure rate with the present study was reported in a study comparing TOT and TVT-O techniques in patients with MUI after three years of follow-up (Abdel-Fattah et al., 2014).

The overall objective long-term cure rates in Studies II and III were 90 % and 89 % after the TVT and TOT procedures, respectively. The results presented here after TVT are in concordance with other studies including patients with MUI with the minimum follow-up of ten years (Aigmueller et al., 2011; Olsson et al., 2010; Reich et al., 2011). There are only two studies apart from present study regarding transobturator tape procedures which include patients with MUI and follow the patients to five years (Groutz et al., 2011; Yonguc et al., 2014). The objective overall success is comparable to ours, even though the outcomes for SUI and MUI patients were not reported separately.

There is no significant decline in the efficacy over time after MUS procedures according to Studies II and III. In Study II the objective outcome declined from 93 % to 90 % between three to 10.5 years of follow-up (Laurikainen and Kiilholma, 2003). After TOT the objective cure was 88 % at three months (Joutsiniemi et al., 2009) and 89 % after the mean follow-up of 6.5 years. No decline was observed after 17 years of follow-up of TVT, whereas a significant decline is detected following Burch colposuspension after the follow-up of 14 years (Kjølhede, 2005; Nilsson et al., 2013). The follow-up time is significantly shorter in studies regarding transobturator techniques compared to retropubic ones. Only one study with the follow-up of more than five years was observed with concordant objective cure rate to the present study (Athanasiou et al., 2013).

In most of the studies regarding mid-urethral sling surgery referred here the patients have undergone UDS preoperatively. In Study II women did not undergo UDS, because this testing was not available at the Turku City Hospital, where the patients were initially operated on. In Study III only 30 % of the patients with a history of overactive bladder symptoms had UDS performed preoperatively. Regardless of the lacking UDS in most of the patients in the present study,

comparable subjective and objective cure rates to other long-term studies including preoperative UDS were observed. The impact of preoperative UDS on the surgical outcome is not explicit, and the results are conflicting. Preoperative maximum urethral closure pressure and Valsalva leak point pressure values may predict postoperative outcomes after surgical treatment for SUI (Porena et al., 2007). Revealing the underlying detrusor overactivity with preoperative UDS in the patients with pure SUI may lead to the avoidance of several surgical procedures (Serati et al., 2013). On the contrary, the routine UDS before surgery to the patients with genuine SUI does not seem to be cost-effective especially if it does not have influence on the plans of the forthcoming surgery, as was concluded in a study where the primary preoperative stress test alone was not inferior compared to the evaluation with UDS and stress test for outcomes at one year (Nager et al., 2012; Weber et al., 2002). The patients with predominant SUI and inconsistent results in UDS did not benefit from individualised treatment compared to immediate surgery (van Leijsen et al., 2013). In the light of the conflicting results regarding preoperative benefit of UDS to the surgical outcome, the patients with genuine SUI or MUI with dominating stress symptoms may possibly be operated on without preoperative UDS with satisfactory outcome.

The objective outcome after MUS seems to be slightly better than the patient's subjective assessment. The physician's expectations of the outcome of the surgery may differ from the patient's opinion and they may be more optimistic for the outcome than that of the patients (Srikrishna et al., 2010). According to the present study the bothersome urgency symptoms significantly decreased the overall quality of life in MUI patients after MUS surgery, this result being confirmed by others (Holmgren et al., 2007). In accordance with the present study, 90 % of the dissatisfied patients had UUI in a study following patients up to seven years after TVT (Reich et al., 2011). The occurrence of UUI and urgency symptoms is increasing along with advancing age (Miedel et al., 2009). After the long-term follow-up a certain proportion of the overactive bladder symptoms may be caused by ageing rather than by the surgical procedure itself. In a population-based survey overactive bladder symptoms increased threefold when comparing women of 40 years of age to women older than 75 years (Milsom et al., 2001). The prevalence of MUI in women >45 years was 36 % in a study conducted in four European countries and it increases with age (Hunskaar et al., 2004). Careful preoperative counselling on the possible time-dependent worsening of the outcome is mandatory to avoid the unrealistic outcome expectations after incontinence surgery especially among the patients with preoperative MUI.

Obesity is known to be a significant risk factor for developing SUI and in addition, obese patients may suffer from more severe urgency, UUI or SUI symptoms than patients with normal weight (Esin et al., 2011; Osborn et al., 2013). In Study III the subjective cure rate according to questionnaires in obese (BMI > 30 kg/m²) patients was significantly inferior compared to patients with BMI ≤30 kg/m² after the TOT procedure. However, subjective satisfaction of the procedure was equal between the groups. It is noteworthy that the improvement in the quality of life among obese patients after the incontinence surgery is significant even if the cure rates are lower than in patients with normal weight (Haverkorn et al., 2011). The objective cure rate was similar between obese and non-obese patients in Study III. This is in concordance with another study of 398 women randomised to undergo retropubic or transobturator incontinence surgery. The patients after TVT and the patients after TOT showed similar objective outcomes in obese and non-obese patients (Rechberger et al., 2010). In addition, an equal outcome in the obese and non-obese patients is reported after transobturator procedures (Esin et al., 2011; Liu et al., 2011). However, after TVT very obese patients (BMI ≥ 35 kg/m²) have significantly lower objective cure rates than women of normal weight and the outcome seems to decline significantly in obese patients over time (Hellberg et al., 2007). Guidance on weight loss among obese incontinence patients is well

justified, particularly because even a moderate weight loss is effective in reducing the symptoms of SUI and UUI (Subak et al., 2009a).

6.3. Outcome of transvaginal mesh surgery

The quality of life is reported to improve significantly after the TVM surgery, and satisfaction on the outcome does not seem to decline throughout the follow-up period of three to five years (de Tayrac et al., 2006; Jacquetin et al., 2013; Miller et al., 2011). Even though some patients suffered from adverse events in the present studies the subjective satisfaction rate was 70.8 % after the mean of one year of follow-up whereas after seven years it was 80.1 %. The relatively high subjective outcome after TVM surgery might reflect the severity of the preoperative symptoms caused by POP. Patient satisfaction and functional outcome after POP surgery are two of the primary end points and should be assessed whenever an outcome of a new surgical technique is evaluated as a whole.

There is no consensus on defining anatomical cure after POP surgery. Therefore, two different definitions were applied in the present study in order to ensure accurate reporting. According to either definition used in Study V the anatomical cure rates were slightly lower compared to previous reports. The overall anatomical cure rate was 56.4 % in Study V whereas cure rates of 67-91 % after three to five years of follow-up have been reported by others when cure is defined as POP-Q stage ≤1 and no re-operations performed due to POP (Benbouzid et al., 2012; de Tayrac et al., 2006; Miller et al., 2011; Nieminen et al., 2010). Higher cure rates are reported in studies defining cure as the leading edge being above the hymen (84-93.3 %) (Gutman et al., 2013; Jacquetin et al., 2013; Wang et al., 2013). Adding also the degree of the descend of the apical compartment in one of the definitions in Study V made the diagnosis of the anatomical recurrence more precise. Especially the anterior Prolift™ has been shown not to give sufficient support to the apical compartment (Hinoul et al., 2008). Therefore, the development of the vaginal mesh surgery has moved to single incision techniques that give additional support to the apical part of the vagina.

It is inevitable that the progressive loss of anatomical support occurs to some degree over time. A significant proportion of women seeking routine gynaecological care have been observed to have some level of vaginal or uterine relaxation, and moreover, 7 % of these women have prolapse at or below hymen (Swift et al., 2005). However, clinically relevant POP symptoms seem to be related to the presence of prolapse descending below the hymen (Barber et al., 2009). Therefore, the commonly used definition POP-Q stage ≤1 for anatomical cure may be too stringent, because a significant proportion of non-symptomatic women do not meet this criterion. The majority of the recurrences meeting the stringent criteria used in the present study was asymptomatic and moreover, reoperations due to POP were required seldom.

The Study V is the longest follow-up published regarding the TVM procedure so far. Maximum prevalence of symptomatic recurrence after AC is found to occur between 18-24 months (Dietz et al., 2014). The more efficient support produced by mesh implant compared to native tissue repair may prolong the time of the appearance of the recurrence, however, a sufficient length of the follow-up is difficult to determine. Two studies following patients up to five years show a slight decline in anatomical cure over time from 88-90 % to 67-84 % (Jacquetin et al., 2013; Miller et al., 2011). Supposedly, the need for reoperations due to recurrent POP increases over time. No reoperations were needed after TVM in the treated compartment in the studies with three years of follow-up whereas after five years the reoperation rate was 3-5 % (Benbouzid et al., 2012; de

Tayrac et al., 2006; Jacquetin et al., 2013; Miller et al., 2011; Nieminen et al., 2010; Wang et al., 2013).

The robust support of the mesh and the altered forces in the pelvic floor might result in increased pressure in the adjacent compartment resulting in subsequent prolapse. The recurrence rate in the untreated compartment other than initially corrected is fairly high after POP surgery and it is higher after TVM than after AC (Withagen et al., 2012). Surgery for the anterior prolapse results in more recurrent prolapses than the posterior correction of POP. It may be crucial to identify and treat apical prolapse in order to prevent recurrence in the untreated compartment. An interaction between the apical connective tissue support and the levator ani muscle impairments in the presence of the anterior vaginal wall prolapse was observed using a biomechanical model (Chen et al., 2006). Combining the anterior mesh procedure with the apical repair significantly diminish *de novo* recurrence in the adjacent compartment (Withagen et al., 2012). The mesh which is anchored to the sacrospinous ligaments in both the anterior and posterior procedures in order to produce apical support may reduce *de novo* prolapses in the adjacent compartment, however, the long-term data regarding this technique is lacking (Stanford et al., 2013).

6.4. Complications after mesh-augmented surgery

De novo SUI symptoms were reported by 187 out of 1,280 women (15 %) after prolapse surgery according to a review (Maher et al., 2010). In Study IV *de novo* SUI was detected in 20 (20 %) patients and 16 underwent an incontinence procedure during the first year after the initial surgery. The incidence of new-onset SUI varies in the short-term reports between 3.9 and 23 % of the patients after TVM (Hiltunen et al., 2007; Nair et al., 2011; Stanford et al., 2013). It is difficult to diagnose occult SUI preoperatively in women with POP and there is no standardised method for it. *De novo* SUI rate of 25 % was observed after total TVM in patients with a negative preoperative stress test combined with prolapse reduction during an urodynamic study (Kasturi et al., 2011). Significant risk factors were not found, however, there was a tendency towards a more robust anterior wall support among patients with *de novo* SUI. The effective correction or even an overcorrection of the urethra and bladder neck with the mesh may unmask the pre-existing SUI (Altman et al., 2011). In a prospective study comparing AC to TVM *de novo* SUI rates were 10 % and 23 % after AC and TVM, respectively (Hiltunen et al., 2007). Careful patient counselling before POP surgery is recommended to prevent disappointing outcomes caused by *de novo* symptoms.

Mesh exposure is a rare complication after the MUS procedures. In the present study one tape exposure into the bladder and one into the vagina were observed after the long-term follow-up. Others have reported similar low exposure rates after the follow-ups of five to 17 years (Angioli et al., 2010; Laurikainen et al., 2014; Nilsson et al., 2013; Svenningsen et al., 2013). However, the same polypropylene mesh used in the vaginal POP surgery induces significantly more exposures through the vaginal epithelium: in 5.3-19 % of the patients during five years of follow-up (Benbouzid et al., 2012; Jacquetin et al., 2013; Miller et al., 2011). Persistent exposures were detected in 0-8.5 % of the patients; however, all these were asymptomatic. It is noteworthy that these reports did not include any late-onset exposures at the time of follow-up while in the present study 72 % out of 36 exposures appeared after the two to three months assessment.

Possibly, the meshes were not placed deep enough under the fibromuscular layer during the procedures presented in Study V, which may lead to insufficient tissue thickness to cover the mesh and to prevent exposures. The overall mesh exposure rate in the present study is comparable with the results in a study were a self-tailored mesh was implanted sub-epithelially (Nieminen et al.,

2010). However, they did not observe any late-onset exposures after the sub-epithelial replacement of the mesh. Surgical technique utilised and the surgeon's experience are regarded as significant risk factors for mesh exposure (Davila and Jijon, 2012; Fatton et al., 2007). The high exposure rate observed in Study V addresses the importance of extensive training when novel, advanced surgical techniques are adopted.

It is not possible to conclude the cause for the high late-onset exposure rate observed in the study presented here. Concurrent hysterectomy is reported to raise the risk for the occurrence of mesh exposure (Collinet et al., 2006; Hiltunen et al., 2007). An exposure rate of 19 % was reported in a study where 21.2 % of the patients had had concomitant hysterectomy performed, however, concluding that there was no association between the concomitant surgery and the exposures (Miller et al., 2011). On the contrary, a low exposure rate of 6.3 % was reported in a study after TVM combined with hysterectomy (Wang et al., 2013). However, any conclusion on the correlation of hysterectomy and exposure rate in Study V cannot be drawn, because only four patients underwent concomitant hysterectomy in the study.

Other identified risk factors for mesh exposure, such as age, refraining vaginal oestrogen use, previous prolapse surgery, postoperative hematoma and concomitant procedures, (Davila and Jijon, 2012), did not have impact on the occurrence of mesh exposure in the present study. The long-term follow-up after a mesh surgery may lead to increasing detection of exposures over time. This was confirmed in a study assessing the outcome and the complications after open SCP (Nygaard et al., 2013). The Prolift™ mesh was relatively large in the area resulting in increased exposure of the mesh material to the tissues. Increased mesh burden has been shown to have an effect on the connective tissue metabolism resulting in impaired mechanical properties of the tissue (Junge et al., 2012). After the withdrawal of Prolift™ from the market the one-incision mesh used widely nowadays is smaller in area than the mesh used in the present study. Exposure rates using one-incision mesh have reported to be 6.5-6.8 % after one year (Lukban et al., 2012; Stanford et al., 2013). By reducing the amount of mesh material utilised in TVM surgery may decrease the occurrence of the mesh exposures.

Most of the exposures observed in present study were asymptomatic. Clinically relevant exposures seem to occur in short-term, and they are treatable. There were no serious mesh-related complications during the long-term follow-up in present study. Although the mesh exposure rate was relatively high, the removal of the implanted mesh was not needed. The overall decline in complications over time persists.

6.5. Recommendations for clinical practice

Surgical treatment for female stress urinary incontinence may be conducted after failed conservative methods, such as weight loss and pelvic floor muscle training (Dumoulin et al., 2014; Subak et al., 2009b). Physiotherapy may be advantageous in treating SUI or SUI predominant MUI. However, the occurrence of predictive factors for poor outcome in physiotherapy (Hendriks et al., 2010) or the patient's lack of motivation for physiotherapy justify MUS surgery as first-line treatment. Initial MUS surgery compared with initial physiotherapy has shown to result in higher rates of subjective improvement and subjective and objective cure (Labrie et al., 2013). Routine preoperative UDS may not be necessary in patients with genuine SUI or MUI with dominating stress symptoms. Patients with MUI and obesity need preoperative counselling due to commonly occurring persistent urinary symptoms, which may decrease the quality of life after surgery.

The TVM surgery should be implemented by experienced and trained gynaecologists. Accurate patient selection and careful surgical technique are necessary in order to gain a satisfactory outcome and to minimise adverse events. Precise preoperative counselling regarding reasonable common *de novo* symptoms and complications, such as SUI, and mesh exposures, are recommended.

6.6 Future perspectives

The studies comparing the long-term results of TVM surgery and traditional vaginal POP surgery, are needed. Prospective studies comparing the efficacy and safety of TVM and SCP surgery in the long term would help to clarify the accurate indications for these surgical techniques. Additionally, investigating the effect of the learning curve of the surgeon on the outcome and complications would be advantageous.

In the future the polypropylene mesh in SUI and POP surgery may be replaced by tissue engineered repair material. Before the progress is possible, the complex metabolism of extracellular matrix of connective tissue including the pathogenesis of elastin and collagens needs further research. Research regarding stem cell treatment for SUI has revealed promising efficacy and safety of the treatment in the short-term (Carr et al., 2013). However, further studies are needed to confirm these results in the long-term before the development of this novel and expensive treatment is feasible.

7. SUMMARY AND CONCLUSIONS

The occurrence of alterations in the connective tissue of women with and without pelvic organ prolapse as a function of clinical factors was performed in order to clarify the multifactorial etiology of pelvic organ prolapse. The long-term subjective and objective outcomes and complications of mesh-augmented vaginal surgery were assessed in four studies. Two studies assessed the outcome and complications of the TVT and TOT procedures after the mean of 10.5 and 6.5 years, respectively. The evaluation of outcome and complications of TVM were carried out with two studies: one assessing the short-term outcome, patient satisfaction and complications while the other study covered the outcome and complications after the median follow-up of seven years.

In conclusion, the present study showed alterations in the elastin and collagens I, III and V in the connective tissue of the patients with POP compared to the controls. These changes in the fibroelastic composition of the connective tissue in the vaginal wall may indicate an increased turnover of elastin fibres and impaired mechanical properties of the connective tissue.

The TVT and TOT procedures showed high overall subjective outcome after long-term follow-up, and in addition, the objective outcome was good even though most of the patients had not undergone preoperative urodynamic studies. The subjective outcome after TVT and TOT was inferior in patients operated on because of MUI and in patients with BMI>30 compared to patients operated on because of SUI and with BMI≤30. Long-term complications were rare. The patients with MUI and obesity may benefit from careful preoperative counselling regarding possible persistent urgency symptoms postoperatively.

The TVM procedure showed good subjective and moderate anatomical outcomes after long-term follow-up. Reoperation rate due to recurrent POP was at an acceptable level. Mesh exposure occurred in nearly one fourth of the patients undergone TVM, however, they were mostly asymptomatic and of late onset.

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10. APPENDICES

10.1. Detrusor Instability Score, Urinary Incontinence Severity Score and VAS

ONKO TEILLÄ VIRTSANKARKAILUA? Kyllä □ Ei □

Jos teillä on virtsankarkailua, niin vastatkaa oheisiin kysymyksiin ympyröimällä vastaus.

	0	1	2
Kuinka monta virtsaamiskertaa Teillä on päiväaikaan?	5 - 7	8 – 10	11 -
Kuinka monta kertaa joudutte öisin nousemaan virtsalle?	0 - 1	2 - 3	4 -
Jääkö rakkoon virtsaa virtsaamisen jälkeen?	Ei	Joskus	Usein
Aiheuttavatko kiire tai jännitys virtsapakkoa?	Ei	Lievää	Voimakasta
Karkaako virtsa ponnistaessa (esim. yskäisy)?	Kyllä	Joskus	Ajoittain muutoinkin
Karkaako virtsa välittömästi ponnistuksen yhteydessä?	Heti	En osaa sanoa	Ponnistuksen jälkeen
Tunnetteko virtsaamistarvetta ennen virtsan karkaamista?	Ei	Joskus	Usein
Kuinka paljon virtsaa karkaa kerralla?	Tippoja	Lirahdus	Virtsa alkaa valua
Kykenettekö keskeyttämään virtsaamisen?	Kyllä	Melko hyvin	Ei
Onko Teillä ollut virtsatietulehduksia viimeisten 2 vuoden aikana?	Ei	1 – 2	3 -

Erotusdiagnostiikka (lääkäri merkitsee): > 8 rakon instabiliteetti, < 6 ponnistusinkontinenssi ☐

	0	1	2
Karkaako virtsa ilman ponnistusta ja asennosta riippumatta (esim. makuulla)?	Ei	Joskus	Hyvin usein
Karkaako virtsa vähäisessä ponnistuksessa (esim. seisomaan noustessa)?	Ei	Joskus	Hyvin usein
Karkaako virtsa yhtäkkisessä voimakkaassa ponnistuksessa (esim. aivastaessa tai juostessa)?	Ei	Joskus	Hyvin usein
Haittaavatko oireet jokapäiväisiä askareitanne?	Ei	Joskus	Hyvin usein
Haittaavatko oireet ansiotyötänne?	Ei	Joskus	Hyvin usein
Pelkäättekö, että muut huomaavat virtsan karkaamisen aiheuttaman hajun ja märkyyden?	Ei	Joskus	Hyvin usein
Haittaavatko oireet harrastuksianne ja menojanne?	Ei	Joskus	Hyvin usein
Haittaavatko oireet sukupuolielämäänne?	Ei	Joskus	Hyvin usein
Ärtyvätkö ulkosynnyttimenne?	Ei	Joskus	Hyvin usein
Joudutteko käyttämään siteitä tai vaippoja	Ei	Joskus	Hyvin usein

Haitta-aste (lääkäri merkitsee): > 10 huomattava haitta, < 5 intensiivihoito ei perusteltua ☐

Kuinka paljon haittaa virtsan karkailusta on teille? merkitkää rasti (X) viivalle

●----------●

Ei lainkaan **Erittäin paljon**

10.2. Colorectal-anal questionnaires and VAS

ONKO TEILLÄ ULOSTEEN KARKAILUA? Kyllä ☐ Ei ☐

Jos Teillä on ulosteenkarkailua, vastatkaa oheisiin kysymyksiin laittamalla rasti (X) sopivaan kohtaan.

	0 **Ei koskaan**	**1** **Harvemmin kuin kerran kuukaudessa**	**2** **Kuukausittain**	**3** **Viikoittain**	**4** **Päivittäin**
Karkaako kiinteä uloste?					
Karkaako löysä uloste?					
Karkaako ilma?					
Käytättekö housunsuojaa ulosteenkarkailun vuoksi?					
Haittaako ulosteenkarkailu elämänlaatuanne ja sosiaalista elämäänne?					

Wexner luokka (lääkäri merkitsee): ≥ 9 heikentää elämänlaatua ☐

Kuinka paljon haittaa ulosteenkarkailusta on teille?
Merkitkää rasti (X) viivalle

●----------●

Ei lainkaan **Erittäin paljon**

ONKO TEILLÄ UMMETUSTA TAI ULOSTAMISVAIKEUTTA? **Kyllä** ☐ **Ei** ☐

Jos Teillä on ummetusta tai ulostamisvaikeutta, vastatkaa oheisiin kysymyksiin laittamalla X sopivaan kohtaan

	Kyllä	**Ei**
Ulostan alle kolme kertaa viikossa		
Käytän ulostuslääkkeitä		
Ulosteeni ovat kovia		
En tunne ulostamisen tarvetta		
Joudun kovasti ponnistelemaan ulostaessani		
Tunnen esteen tunnetta yrittäessäni ulostaa		
Joudun ulostamaan useita kertoja peräkkäin ja ulostetta jää peräsuoleen		
Joudun sormilla painamaan peräsuolen ulkopuolelta tai kaivamaan/poistamaan ulostetta		

Drossman kriteeri posit.(lääkäri merkitsee): ulostaminen ≤ 3 x vrk +/- ponnistus yli ¼ ulostamisajasta ☐

Kuinka paljon haittaa ummetuksesta/ulostamisvaikeudesta on teille? Merkitkää rasti (X) viivalle

●----------●

Ei lainkaan **Erittäin paljon**

Oletteko tyytyväinen teille tehtyyn laskeumaleikkaukseen? **Kyllä** ☐ **Ei** ☐

10.3. The Urogenital Distress Inventory-6

Olkaa hyvä ja rastittakaa oireisiinne parhaiten sopiva ruutu:

Esiintyykö Teillä seuraavia oireita ja miten hankalina?	ei lainkaan	hieman	kohtalaisesti	suuressa määrin
Tihentynyt virtsaamistarve				
Virtsankarkailua, johon liittyy pakottava virtsaamistarve				
Virtsankarkailu liittyen ponnistustilanteisiin, yskimiseen tai aivastamiseen				
Virtsa karkaa tipoittain, pieniä määriä				
Hankaluuksia tyhjentää rakkoa				
Kipuja alavatsalla tai ulkosynnyttimien alueella				

10.4. Incontinence Impact Questionnaire-7

Olkaa hyvä ja rastittakaa oireisiinne parhaiten sopiva ruutu:

Onko virtsankarkailu vaikuttanut:	ei lainkaan	hieman	kohtalaisesti	suuressa määrin
Kotiaskareisiinne				
Liikuntaharrastuksiinne				
Muihin harrastuksiinne				
Matkustamineen (>30 min matka kotoa)				
Sosiaaliseen kanssakäymiseen				
Tunne-elämäänne (mm. hermostuminen, masentuneisuus)				
Aiheuttanut turhautumisen tunnetta				

10.5. EuroQoL-5D

EQ-5D

Terveyskysely (Suomalainen versio)

Olkaa hyvä ja merkitkää rastilla (x), yksi rasti kunkin alla olevan ryhmän kohdalle, mikä seuraavista kolmesta väitteestä kuvaa parhaiten terveydentilaanne tänään:

Liikkuminen
( ) Minulla ei ole vaikeuksia kävelemisessä
( ) Minulla on jonkin verran vaikeuksia kävelemisessä
( ) Olen vuoteenomana

Itsestä huolehtiminen
( ) Minulla ei ole vaikeuksia huolehtia itsestäni
( ) Minulla on jonkin verran vaikeuksia peseytyä tai pukeutua itse
( ) En kykene peseytymään tai pukeutumaan itse

Tavanomaiset toiminnot
( ) Minulla ei ole vaikeuksia suorittaa tavanomaisia toimintojani (esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot)
( ) Minulla on jonkin verran vaikeuksia suorittaa tavanomaisia toimintojani
( ) En kykene suorittamaan tavanomaisia toimintojani

Kipu tai vaiva
( ) Minulla ei ole kipuja tai vaivoja
( ) Minulla on kohtalaisia kipuja tai vaivoja
( ) Minulla on ankaria kipuja tai vaivoja

Mieliala
( ) En ole ahdistunut enkä masentunut
( ) Olen melko ahdistunut tai masentunut
( ) Olen erittäin ahdistunut tai masentunut

Verrattuna keskimääräiseen terveydentilaani viimeisten 12 kuukauden aikana, terveydentilani tällä hetkellä on

( ) Parempi
( ) Suunnilleen sama
( ) Huonompi

10.6. Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire short form

Oletko seksuaalisesti aktiivinen? □ Olen □ En ole

Onko tahaton virtsan karkailu tai onko laskeuma vaikuttanut seuraaviin asioihisi?

	Aina	Usein	Joskus	Harvoin	Ei koskaan
Kuinka usein tunnet seksuaalista halukkuutta?	□	□	□	□	□
Saatko orgasmin yhdynnässä kumppanisi kanssa?	□	□	□	□	□
Tunnetko kiihottuvasi seksin aikana?	□	□	□	□	□
Oletko tyytyväinen seksielämääsi nykyisessä elämäntilanteessasi?	□	□	□	□	□
Tunnetko kipua seksin aikana?	□	□	□	□	□
Onko Sinulla virtsankarkailua yhdynnän aikana?	□	□	□	□	□
Rajoittaako karkailun pelko seksielämääsi?	□	□	□	□	□
Vältätkö yhdyntöjä laskeuman pullistumisen vuoksi?	□	□	□	□	□
Huomaatko negatiivisia tunteita itsessäsi seksin aikana, kuten pelkoa, inhoa, häpeää tai syyllisyyttä?	□	□	□	□	□
Onko kumppanillasi erektiovaikeuksia jotka haittaa seksielämäänne?	□	□	□	□	□
Onko kumppanillasi ongelmana ennenaikainen siemensyöksy, joka vaikuttaa seksielämäänne?	□	□	□	□	□
Kuinka intensiivisiä orgasmisi ovat olleet viimeisen 6 kuukauden aikana verrattuna aiempaan?	□	□	□	□	□

10.7. Pelvic Organ Prolapse Distress Inventory

Syntymäaika tai nimi:_____

Pituus_____Paino_____ Tupakointi: Ei □ Kyllä □

1.Tunnetko yleensä painon tunnetta alavatsalla?

En □ Kyllä □

Jos vastasit kyllä, kuinka paljon tämä haittaa sinua?

ei yhtään □ hiukan □ kohtalaisesti □ paljon □

2. Tunnetko yleensä painon tunnetta tai onko Sinulla tunnottomuutta lantion alueella?

Jos vastasit kyllä, kuinka paljon tämä haittaa sinua?

ei yhtään □ hiukan □ kohtalaisesti □ paljon □

3. Oletko viime aikoina tuntenut tai nähnyt jotakin pullottavan tai pullistuvan ulos emättimestäsi?

Jos vastasit kyllä, kuinka paljon tämä haittaa sinua?

ei yhtään □ hiukan □ kohtalaisesti □ paljon □

4. Täytyykö Sinun yleensä auttaa ulostamista painamalla sormin peräsuolta emättimen puolelta tai peräsuolen ympäriltä? Ei □ Kyllä □

Jos vastasit kyllä, kuinka paljon tämä haittaa sinua?

ei yhtään □ hiukan □ kohtalaisesti □ paljon □

5. Tuntuuko Sinusta, että virtsarakko ei tyhjene täysin virtsaamisen yhteydessä?

Ei □ Kyllä □

Jos vastasit kyllä, kuinka paljon tämä haittaa sinua?

ei yhtään □ hiukan □ kohtalaisesti □ paljon □

6. Täytyykö Sinun yleensä auttaa virtsaamista painamalla sormin emättimen etupuolta?

Jos vastasit kyllä, kuinka paljon tämä haittaa sinua?

ei yhtään □ hiukan □ kohtalaisesti □ paljon □

7. Onko Sinulla jokin seuraavista perussairauksista?

a. verenpainetauti □
b. sepelvaltimotauti □
c. diabetes □
d. kilpirauhasen vajaatoiminta □
e. astma □
f. keuhkoahtaumatauti □
g. reuma tai muu sidekudossairaus □
h. muistisairaus □
i. sairastettu syöpä, mikä_____

8. Onko Sinulla käytössä jokin seuraavista lääkkeistä?

a. insuliini □
b. verenohennuslääke, mikä_____
c. verenpainelääke □
d. kortisoni □
e. reumalääke □
f. virtsarakkoa rauhoittava lääkitys □

10.8. Questionnaire Study III

Onko Teillä ollut leikkauksen jälkeen

1. Tulehduksia:

– virtsatietulehduksia kyllä / ei (jos on, montako_____)

2. Tihentynyttä virtsaamisen tarvetta:
– ei lainkaan / saman verran / enemmän kuin ennen leikkausta
– jos on, virtsaamiskertojen määrä päivällä____ yöllä____
− mitä hoitoa olette saaneet (esim. lääkkeen nimi)_____

3. Hankaluuksia virtsarakon tyhjentämisessä? kyllä / ei

4. Muuta ongelmaa virtsaamiseen liittyen, tai onko tehty jatkoleikkauksia (esim. nauhan katkaisu)
_____

5. Karkaako virtsa **ponnistustilanteissa** verrattuna ennen leikkausta olleeseen tilanteeseen:

− enemmän
− saman verran
− vähemmän

6. Karkaako virtsa **ei-ponnistustilanteissa** : kyllä / ei

7. Käytättekö vaippoja virtsankarkailun vuoksi:

kyllä / ei onko vaipoissa virtsaa?_____

8. Oletteko tyytyväinen leikkaustulokseen:

en / melko tyytyväinen / tyytyväinen

Miksi ette ole tyytyväinen ?_____

9. Suosittelisitteko toimenpidettä ystävällenne: kyllä / ei

Kiitos vastauksestanne!

10.9. Questionnaire Study IV

Kyselylomake liittyen laskeumaleikkausten seurantatutkimukseen

Pyydämme Teitä vastaamaan alla oleviin kysymyksiin ympyröimällä yksi tai useampi vaihtoehto tai täyttämään puuttuva kohta

Lomakkeen täyttämispäivämäärä _____

Nimi _____Syntymäaika _____

Käytättekö jotain seuraavista hormonivalmisteista?
1) estrogeenia paikallisesti emättimeen
2) estrogeenia tablettina / laastarina / voiteena
3) yhdistelmähoitoa (estrogeenia ja keltarauhashormonia)
4) hormonikierukkaa

Onko Teillä käytössä seuraavia lääkityksiä?
1) kortisonihoito suun kautta annosteltavana
2) insuliinihoito tai diabeteksen tablettimuotoinen hoito
3) nesteenpoistolääkitys (esim. verenpainelääkityksen mukana)
4) toistuviin virtsatieinfektioihin estolääkitys

Mitä oireita Teillä oli ennen laskeumaverkkoleikkausta? Ympyröikää oire/oireet ja alleviivatkaa näistä hallitsevin tai vaikein oire.

1) painon tunne
2) hankaluus rakon tyhjentämisessä
3) ponnistukseen liittyvä virtsankarkailu
4) kiire ehtiä virtsaamaan
5) tihentynyt virtsaamistarve
6) ilman tahaton karkaaminen
7) ulosteenkarkailu
8) hankaluus peräsuolen tyhjentämisessä
9) yhdyntäkivut
10) muu kipu

Paranivatko vaivat leikkauksella?

1) kyllä 2) ei, mikä oire jäi _____

Onko Teille ilmaantunut uusia oireita leikkauksen jälkeen ?
1) painon tai pullistuman tunne alapäässä
2) kiristystä esim. istuessa
3) virtsankarkailua liittyen ponnistukseen
4) virtsankarkailua liittyen virtsapakkoon
5) tihentynyttä virtsaamistarvetta
6) vaikeus rakon tyhjentämisessä

7) virtsaamiskipua
8) ulosteenkarkailua
9) ulostamiskipua

10) vaikeus suolen tyhjentämisessä
11) yhdyntäkipua
12) muuta kipua, mitä _____

Oletteko seksuaalisesti aktiivinen / onko Teillä yhdyntöjä ?
1) kyllä 2) ei

Onko Teille ilmaantunut verkkoleikkauksen jälkeen kipua tai kirvelyä yhdynnässä ?
1) ei 2) joskus 3) usein 4) aina

Muita ongelmia yhdynnässä
1) tunnottomuutta 2) emättimen ahtaus 3) muuta, mitä _____

Onko Teille tehty tai suunnitteilla verkkoleikkauksen jälkeen gynekologinen uusintaleikkaus ?
1) ei 2) kyllä, mikä _____

Oletteko tyytyväinen leikkaustulokseen?
1) kyllä 2) ei 3) en osaa sanoa

Suosittelisitteko leikkausta ystävillenne ? 1) kyllä 2) ei