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TRANSVAGINAL MESH FOR PELVIC ORGAN PROLAPSE - CLINICAL AND HISTOLOGICAL ASPECTS

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Stockholm 2012

Published by Karolinska Institutet.

ISBN 978-91-7457-704-4

Printed by


www.reproprint.se
Gårdsvägen 4, 169 70 Solna

ABSTRACT

The objectives of this thesis were to assess the objective, clinical, and sexual outcomes after transvaginal surgery for pelvic organ prolapse using a trocar guided mesh kit, to ascertain the vaginal in vivo histological inflammatory response to large mesh, and to identify possible risk factors associated with exposures after transvaginal mesh surgery.

A prospective multicenter cohort study was performed between June 2006 and March 2007 throughout 26 clinics in the Nordic countries. The 261 women included underwent pelvic organ prolapse surgery with the Prolift® mesh kit and were examined at baseline, two months and one year regarding objective anatomic prolapse stage, signs of vaginal inflammation and subjective symptom assessment. We found satisfactory anatomic cure rates (between 79 and 86%), few serious complications (3.4%) and exposures in 11%. Subjective improvements were seen in both questionnaire scores though not specifically for stress urinary incontinence.

Among women undergoing the above prospective multicenter cohort study, sexually active women were separately analyzed with regard to sexual function before and one year after surgery using a specific questionnaire. Overall symptom scores deteriorated at one year after surgery irrespective of the surgically corrected compartment and of anatomical corrective success. The deterioration was attributed primarily to behavioral-emotive and partner related items and not specifically to dyspareunia.

To determine the histological inflammatory response to large vaginal mesh, a histological study was performed. Ten women undergoing prolapse surgery using mesh from the prospective cohort study above underwent vaginal punch biopsy sampling prior to surgery and one year after. The specimens were analyzed microscopically regarding inflammatory response and compared to 8 healthy controls. At one year, a persisting low grade host-implant reaction was seen in patients.

Data from the above prospective cohort study was combined with data from a randomized controlled study comparing transvaginal mesh surgery for anterior prolapse with traditional plication techniques. Only women undergoing anterior repair with mesh were analyzed and potential risk factors for developing exposures were assessed. We found that women who smoked, had given birth to more than two children and who had systemic inflammatory disease had greater odds of developing exposures.

In conclusion, the four studies in this thesis have shown that transvaginal mesh for pelvic organ prolapse provides satisfactory anatomical and subjective cure rates at one year with relatively few serious adverse events. However there are significant risks of deteriorated sexual function (especially in behavioral/emotive and partner related aspects), vaginal non infectious inflammation and mesh exposures. We have shown that women who smoke, have more than two children and suffer from somatic inflammatory disease are at greater risk of mesh exposures. In spite of partly encouraging results, the findings pose significant challenges to the overall success and acceptance of the procedure. Prior to recommending the use of mesh for pelvic floor correction, all available information on symptoms, the nature of the prolapse, surgical short and longterm outcomes as well as potential risks and benefits must be adequately analyzed and considered.

LIST OF PUBLICATIONS

This thesis is based on the following papers, referred to in the text by their roman numeral:

I. Trocar-Guided Transvaginal Mesh Repair of Pelvic Organ Prolapse

Elmér C, Altman D, Ellström Engh M, Axelsen S, Väyrinen T, Falconer C; Nordic Transvaginal Mesh Group.

Obstetrics & Gynecology 2009;113(1):117-26

II. Sexual dysfunction after trocar-guided transvaginal mesh repair of pelvic organ prolapse.

Altman D, Elmér C, Kiilholma P, Kinne I, Tegerstedt G, Falconer C; Nordic Transvaginal Mesh Group.

Obstetrics & Gynaecology 2009;113(1):127-33

III. Histological inflammatory response to transvaginal polypropylene mesh for pelvic reconstructive surgery.

Elmér C, Blomgren B, Falconer C, Zhang A, Altman D.

Journal of Urology. 2009;181(3):1189-95

IV. Risk factors for mesh complications after trocar guided transvaginal mesh kit repair of anterior vaginal wall prolapse

Elmér C, Falconer C, Hallin A, Larsson G, Ek M, Altman D; Nordic Transvaginal Mesh Group

Accepted for publication Urogynecology and Urodynamics 27 Jan 2012

CONTENTS

LIST OF ABBREVIATIONS

Aa	Point A on anterior wall
Ap	Point A on posterior wall
Ba	Point B on anterior wall
Bp	Point B on posterior wall
BMI	Body Mass Index (kg/m^2)
C	Cervix or cuff
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
cm	centimeter
D	Posterior fornix
DP	Dermal papillae
FDA	Food and Drug Administration
gh	Genital hiatus
ICS	International Continence Society
IUGA	International Uroynecological Association
IIQ	Incontinence Impact Questionnaire
Pb	Perineal body
PFMT	Pelvic floor muscle training
PISQ	Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire
POP	Pelvic Organ Prolapse
POP-Q	Pelvic Organ Prolapse Quantification system
RCT	Randomized Controlled Trial
SD	Standard Deviation
SUI	Stress Urinary Incontinence
Tvl	Total vaginal length
TVM	Transvaginal mesh
TVT	Tension free vaginal tape
TVT-O	Tension free vaginal tape - obturator
UDI	Urinary Distress Inventory

1 INTRODUCTION

Pelvic organ prolapse is reported in up to 50% of parous women,(1) with a reported lifetime risk of undergoing pelvic reconstructive surgery around 11%.(2) However, after traditional prolapse surgery recurrence rates up to 58%,(3) have been reported. Inspired by success in mesh assisted sling procedures for stress urinary incontinence, a rapid and widespread transition from traditional pelvic organ prolapse surgery to surgical techniques using biomaterials has transpired, the aim of which is to improve the durability and tensile strength of anatomic restoration and to improve on the often unsatisfactory surgical outcomes after prolapse corrective surgery.(4)

The unique vaginal microenvironment, dynamics, biochemical exchange and immunological response to some extent prevents the generalisability of results from animal studies, or other areas of biomaterial use, such as inguinal hernia surgery to the pelvic floor.(5) When used for the tension-free vaginal tape (TVT) procedure, macroporous, monofilament, polypropylene mesh has shown advantageous properties as compared with other synthetic biomaterials.(6, 7) As a result, polypropylene mesh has become the most commonly marketed biomaterial for use in and pelvic organ prolapse surgery.

It has been suggested that in order for biomaterials to provide the intended pelvic floor support, they need to be "anchored" outside the afflicted tissues.(8) This has given rise to trocar-guided transvaginal surgical techniques using a transobturator or transgluteal approach, passing mesh fixation arms through the arcus tendineus fascia pelvis or the sacrospinous ligaments.(8) Studies on perioperative morbidity and short-term clinical outcomes using trocar-guided mesh kits have yielded promising objective and subjective clinical outcomes.(9-12)

Increasing the surface size and adding points of fixation may alter the biomechanical characteristics of the mesh. The introduction of larger mesh may also change the histological and inflammatory response of the vaginal tissues to the implant as compared to the small sized tapes used for stress urinary incontinence surgery. Many important long term outcome measures have not yet been accounted for and mesh related complications are a significant cause of morbidity. Adverse mesh reactions such as exposure, infection, pain and sexual dysfunction are of major concern in relation to the use of foreign body materials for pelvic reconstructive surgery.(13) The favorable outcomes associated with the use of polypropylene mesh for the TVT procedure cannot be assumed valid also for other areas of pelvic surgery. Due to the lack of clinical safety and efficacy data use of polypropylene mesh for pelvic organ prolapse surgery remains a source of controversy and further clinical research has been called for.(13-15)

2 BACKGROUND

2.1 ANATOMY

2.1.1 Embryology of the urogenital system

Although genetic sex is predetermined at fertilization the gender is not apparent until the 7th week of embryonic life and is dependent on the testis-determining factor (TDF), encoded on the Y chromosome. The basic developmental path is female, not requiring estrogen but rather the absence of testosterone. The urinary and genital systems develop from the mesodermal layer and are closely related. In the 5th week, the cloaca is formed from a mesodermal fold. It is then divided by the urorectal septum into the posterior anorectal canal and the anterior urogenital sinus from which the bladder and urethra form.

The ovaries originate from germ cells proliferating in the genital ridges at the 6th week, to where they have migrated from the wall of the yolk sac. Initially there are two pairs of genital ducts; the mesonephric ducts from which the ductus deferens, epididymis and the seminal vesicle form in the male, and the partially fused Müllerian or paramesonephric ducts from which the uterovaginal canal and fallopian tubes, as well as broad ligament form in the female. During the 7th developmental week, hormones initiate the domination of one duct. The distal fusion of the paramesonephric ducts occurs at the anterior urogenital sinus in the 8th to 11th week and bring together folds of the peritoneum creating the broad ligament and dividing the pelvic cavity into the posterior rectouterine and anterior vesicouterine pouch.(16, 17)

2.1.2 The female pelvic floor organs

2.1.2.1 The bony pelvis

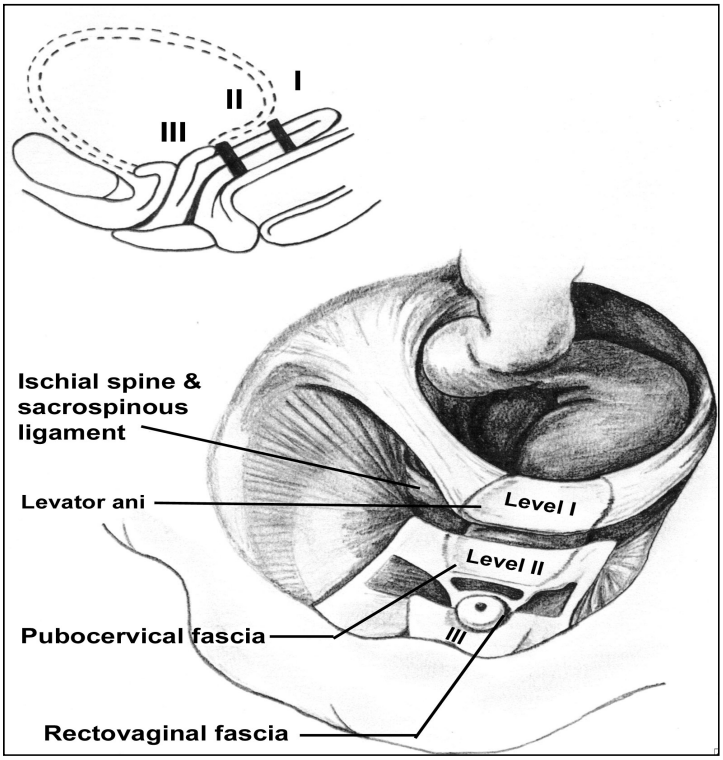
The female pelvic floor organs are enclosed in the skeleton of the pelvis which is made up of the sacrum and coccyx, and the paired hip bones (os coxae) which fuse anteriorly at the symphysis pubis. Important landmarks on the hip bones are the ischial spine which is the point of fixation for the sacrospinous ligament, and the obturator foramen covered on the inside with the obturator muscle and through which obturator nerves and vessels are transmitted cranially.

2.1.2.2 The vagina and its support

The vagina is a hollow and elastic cylinder extending from the vulvar vestibule to the uterus and is suspended most cranially to the paracolpium (endopelvic fascia surrounding the cervix). DeLancey described three levels of vaginal support where the most cranial attachments are named Level I. In the mid portion, Level II, the vagina is attached ventrally and laterally to the thickened endopelvic fascia and the tendineus arch and levator via the arcus tendineus fascia pelvis. Lateral detachments of the vagina can be seen in some anterior prolapse and cystocele formation. In the distal portion, Level III, the vagina is fused to the medial surface of the levator ani muscles, urethra, and perineal body. The vagina's axis is almost horizontal in the upright position, and lies ventral to the lower rectum and anal canal, and posterior to the bladder and urethra. The fibromuscular vaginal wall incorporates anteriorly the pubocervical and posteriorly the rectovaginal fascias which consist of condensations of connective tissue and smooth

muscle rather than fibrous tissue as the name would suggest. The perineal body is the hub or center of the superficial part of the pelvic floor, connecting the perineal membrane, the transverse superficial perineal muscle, bulbocavernous muscle and pubovisceral muscle as well as the anal sphincter and posterior vaginal wall.

Figure 1. Levels of vaginal support as described by DeLancey



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2.1.2.3 The bladder and urethra

The bladder is a spherical organ whose base, or trigonal area, lies ventrally to the anterior vagina and whose lateral sides are confined by the levator ani and internal obturator muscle. The trigone is involved in the regulation of continence and has primarily sympathetic innervation. The internal urethral orifice forms the third corner of the trigone (together with the two ureteral orifices) and the urethra then extends, surrounded by endopelvic fascia, 3-4 cm to the vulvar vestibule anterior to the vagina. Inner longitudinal and circular smooth muscle fibers are found along the urethra, as well as, circular skeletal muscle fibers most densely found in the midurethral segment forming the sphincter urethrae. The urethral sphincter provides resting muscle tone and passive continence. Voluntary or reflex continence, however, is provided by contraction of the puborectalis muscle as a response to suddenly raised intra-abdominal pressure. These basic principles of urinary continence do, however, remain incompletely understood and other intricate mechanisms such as tensile support of the urethra may also be involved in the maintenance of continence.

2.1.2.4 The muscles and ligaments of the pelvic floor

The muscles of the proper pelvic floor form a broad trampoline like suspension of the intra-abdominal cavity with perforations for the rectum, vagina and urethra. It is made up of the levator ani (incorporating the pubovaginalis, puborectalis, and iliococcygeus muscels), and is attached at the sides to the tendineus arch. The tendineus arch (or arcus tendineus) is often described as a densification of the fascia covering the obturator muscle on the inside of the obturator foramen extending from the pubis to the ischial spine, stretching from the pubis anteriorly to the coccyx posteriorly. During contraction the horse shoe shaped tendineus arch compresses the rectum, vagina and urethra towards the pubis.

The arcus tendineus fascia pelvis is a caudal section of the tendineus arch providing attachment for the vagina laterally and ventrally. The cardinal ligaments attach to the sides of the cervix and extend laterally, the sacrouterine ligaments attach circularly round the cervix and extend bilaterally to the sacrum and both cardinal and sacrospinous ligaments fixate the uterus in place. The pubourethral and pubovesical ligaments attach to the urethra/bladder and extend to the pubis fixating these organs.

2.1.2.5 The endopelvic fascia

The endopelvic fascia is a supportive fascial structure surrounding the organs and structures in the pelvic floor, providing attachment between them, in certain places becoming dense (sacrouterine ligaments) and in others membranous (urogenital diaphragm). It is largely made up of smooth muscle and is therefore flexible and not passively rigid.

2.1.3 Normal vaginal histology

A mucous membrane is a functional unit lining cavities which connect with the outside of the body. The human vaginal wall consists of a mucous membrane, a muscular layer (muscularis mucosae) and an outer adventitia. The mucous membrane or mucosa consists of an outer layer of stratified squamous epithelium measuring 150 to 200 μm in thickness and an underlying supportive connective tissue layer (lamina propria) whose papillae project into the undersurface of the epithelium. The basal lamina or basement layer separates the epithelium from the underlying lamina propria. The squamous epithelium is generally not keratinized and therefore nuclei can be seen in epithelial cells throughout the thickness of the epithelium. Growth and accumulation of glycogen in the epithelium is stimulated by estrogens and the continuous desquamation of the most superficial cells allows their analysis in vaginal smears.

In the dense outer region of the connective tissue layer or lamina propria, abundant elastic fibers and collagen are found, allowing for stretch and expansion in conjunction with childbirth. Fibroblasts are found scattered in the connective tissue where they are responsible for the synthesis of collagen and elastic fibers. In the deeper and less dense ‘submucosal’ region abundant blood vessels are found. Inflammatory cells such as lymphocytes and leukocytes are spread out in the connective tissue.(18) The muscularis mucosa consists of smooth muscle in an inner circular and an outer thicker longitudinal layer and the adventitia which is the deepest part consists of dense connective tissue

and an outer looser layer which connects with the adventitiae of surrounding structures, becoming part of the endopelvic fascia.

2.2 PELVIC ORGAN PROLAPSE

Pelvic organ prolapse is a benign condition where the vaginal walls descend, bulge and eventually protrude out of the vagina. The ICS definition stipulates pelvic organ prolapse involves: *"The descent of one or more of: the anterior vaginal wall, the posterior vaginal wall, and the apex of the vagina (cervix/uterus) or vault (cuff) after hysterectomy."*

2.2.1 Epidemiology

Pelvic organ prolapse is a common disorder reflected by the large number of reconstructive procedures performed yearly. More than 300,000 prolapse procedures were performed in the United States in 2003, a number that has increased from just over 225,000 in 1997.(19, 20) In Sweden the corresponding figure for 2010 was almost 8,700 procedures (www.socialstyrelsen.se/statistik). The peak incidence of pelvic organ prolapse surgery occurs in the age group 60-69 years (41.1 per 10 000 women),(21) and the number of parous women who present with pelvic organ prolapse to some extent reaches 50% in some populations.(1) The number of women who report symptomatic pelvic organ prolapse may, however, be as low as 8.3%.(22) These figures indicate that loss of pelvic organ support is present in most women after childbirth and may be considered normal. However, there is no universal consensus on when descensus of the vagina signifies abnormality or dysfunction and motivates intervention.

Approximately 11% of women in industrialized societies undergo surgery for pelvic organ prolapse or urinary incontinence,(2, 23) and after surgery as many as 41-58% have recurrent prolapse. As a consequence 10-29% of women undergo reoperation or secondary procedures.(2, 3, 24) The most common operation for pelvic organ prolapse is the anterior repair. Olsen et al.,(2) found that 40.1% were operated in the anterior compartment only, 7.3% in the posterior compartment only, and 5.7% in the apex only. These figures are reflected by the Women's Health Initiative where cystocele was found in 34% and rectocele in 19% of the participants at clinical examination.(25)

2.2.2 Pathophysiology and Etiology

The different types of prolapse include anterior wall prolapse (cystocele, urethrocele, and paravaginal defects), posterior wall prolapse (enterocele, rectocele, perineal deficiency) and upper vaginal prolapse (uterine prolapse or vaginal vault prolapse after hysterectomy), or a combination thereof. The etiology of pelvic organ prolapse is intricate and not fully understood. Risk factors include vaginal delivery, instrumental delivery, multiparity,(21, 26) raised intra-abdominal pressure (e.g. caused by coughing, straining, overweight),(27) congenital or acquired connective tissue abnormalities,(28) ageing and menopause.(29) It has also been shown that genetic predisposition,(30) and hysterectomy,(31) contribute to the development of prolapse. Based on these reports it is biologically plausible that pelvic organ prolapse has a complex and multifactorial etiology.

2.2.3 Symptoms

Women with prolapse may present a variety of symptoms caused either by the descensus of the pelvic organ themselves or indirectly by the effects of loss of support on the pelvic organs. Pelvic heaviness, vaginal bulging or protrusion, a vaginal globus sensation, lower urinary tract symptoms, bowel emptying difficulties, and sexual dysfunction are common symptoms among women with pelvic organ prolapse.(32, 33) Several symptoms often coexist but aside from vaginal bulging it remains uncertain which symptoms are specific to prolapse.(34) Co-existing urinary incontinence is a particularly common complaint affecting up to 44% of women with pelvic organ prolapse.(35) Incontinence procedures are sometimes performed concurrently with prolapse surgery but the practice is a source of controversy.(36, 37) Other lower urinary tract symptoms frequently associated with pelvic organ prolapse includes a weak urinary stream, urinary retention, and urinary urgency.

2.2.4 Clinical evaluation of prolapse

Diagnosing pelvic organ prolapse in most cases involves a clinical examination which describes vaginal anatomy and topography. In cases with complex clinical findings radiographic assessments such as defecography or MRI may be warranted.(38, 39) Attempts have been made to achieve a global standard description of pelvic organ prolapse but none have been widely accepted until 1996 when the ICS standardization committee introduced the Pelvic Organ Prolapse Quantification system (POP-Q).(40) Previous systems like Porges, Baden-Walker and Beecham are still in use but the POP-Q is currently considered gold standard. (41)

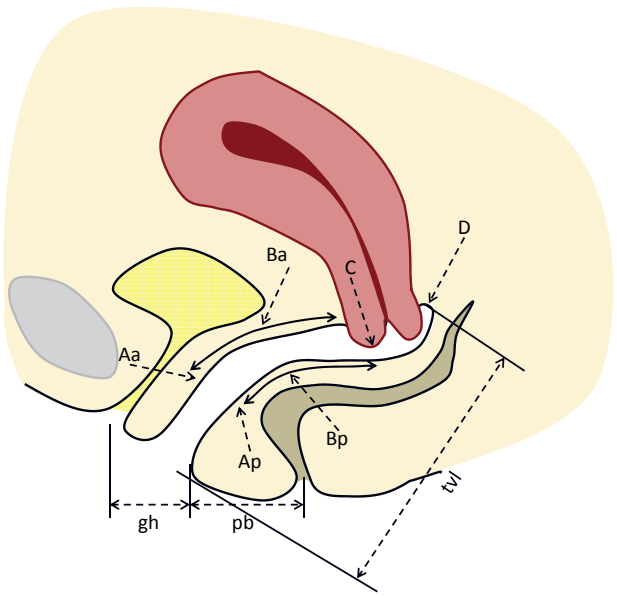
According to the POP-Q, absence of prolapse is defined as stage 0 support on a scale from 0-IV.(42) The position is determined at maximum strain or Valsalva with the patient in a lithotomy position. The hymen is the fixed point of reference defined as point zero (or the zero plane), and the anatomic position of six defined points are measured in centimeters above (negative numbers) or below (positive numbers) the hymen plane. Another three measurements are performed to complete the POP-Q system describing the genital hiatus, the perineum and vaginal length.

Since it is often uncertain which specific organ lies behind the protruding vaginal wall, it is recommended that the prolapse be described according to its pelvic compartment rather than the presumed underlying organ (i.e. anterior wall prolapse instead of cystocele, posterior wall prolapse rather than rectocele). The total of 9 points and landmark measurements included in the POP-Q system are described in Table 1 and Figure 2 below.

Table 1. Landmarks used in POP-Q

Aa: Point 3cm proximal to ext urethral meatus. Possible values: -3cm to +3cm	**Ba:** Point representing most distal position of anterior vaginal wall.	**C:** Point representing most distal edge of cervix/vaginal cuff.
gh: Distance from middle of ext urethral meatus to posterior midline hymen (cm).	**pb:** Distance posterior margin of gh to the midanal opening (cm).	**tvl:** Greatest depth of the vagina when C/D reduced to normal position (cm).
Ap: Point 3cm proximal to the hymen. Possible values: -3cm to +3cm	**Bp:** Point representing most distal position of posterior vaginal wall.	**D:** Point representing posterior fornix/Douglas. (Omitted if patient does not have cervix)

Figure 2. POP-Q measurements

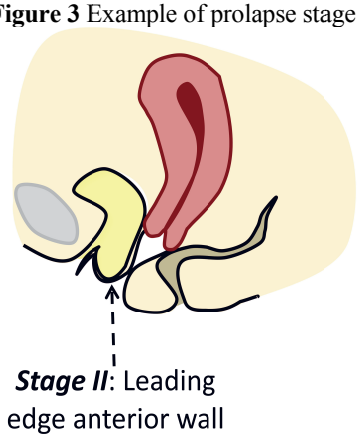


Stages of prolapse are assigned after the quantitative description, as seen in Table 2.

Table 2. Prolapse Stages in POP-Q

Stage 0	No prolapse: Aa, Ap, Ba, Bp = -3cm C, D ≤ -(tvl-2)cm
Stage I	Most distal point < -1cm (<1cm above the hymen)
Stage II	Most distal point ≥ -1cm but ≤ +1cm (from 1cm above to 1cm below the hymen)
Stage III	Most distal point > +1cm but < +(tvl-2)cm (>1cm below the hymen but not more than 2cm less than total vaginal length)
Stage IV	Complete eversion; most distal point ≥ +(tvl-2)cm (protrudes to at least 2cm less than total vaginal length)

Figure 3 Example of prolapse stage II



Aa: -1	**Ba:** -1	**C:** -5
gh: 3	**pb:** 2	**Tvl:** 10
Ap: -3	**Bp:** -3	**D:** -7

2.3 TRADITIONAL MANAGEMENT OF PROLAPSE

2.3.1 History

Treatment of pelvic organ prolapse can be traced as far back as ancient Greece and Egypt. Ancient remedies included astringent solutions, succussion, hanging upside down and vaginal inlays such as a pomegranate.(43) Inlays made of cotton wool were used in the 16th century, other materials like brass and rubber have also been used and these have since developed into modern day pessaries. Surgical treatments evolved in the aftermath of anesthesiologic advancement in the late 19th century with the development of the widespread surgical technique introduced by Donald and Fothergill from Manchester.(44, 45)

2.3.2 Conservative and mechanical methods

Conservative methods of treatment for pelvic floor disorders include pelvic floor muscle training (PFMT), electric stimulation, biofeedback, lifestyle interventions such as weight loss, reducing exacerbating activities (e.g. coughing and lifting) and treating constipation. It is not completely understood how (or if) these methods are valid in the management of prolapse. There are some encouraging results regarding PFMT for symptomatic pelvic organ prolapse,(46) but the evidence is inconclusive. Mechanical devices such as pessaries lift the bulging vaginal walls when lodged between the posterior fornix and the pubis. Most often pessaries are made from plastic or rubber mixes, subsequently they are cheap, but in general pessaries are used in women with milder prolapse, in those who are planning future pregnancies, women waiting for surgery or patients who are unsuitable for surgery.(47)

2.3.3 Traditional Surgical techniques

Surgery is the mainstay for the treatment of pelvic organ prolapse. It has long been believed that surgical repair in one vaginal compartment predisposes a patient to prolapse in others. Consequently, a tradition evolved were pelvic surgeons addressed several potential defects at the same time, hence the historical popularity of the complete Manchester technique. In later years, however, there has been a shift towards operating only the affected compartment and leaving future repair until the need arises.(48) Surgical strategies involve either obliterative (used primarily in elderly women with no wish for sexual activity) and reconstructive techniques.

Reconstructive procedures can be performed by an abdominal, laparoscopic or vaginal approach and may include removal of the uterus (hysterectomy).(49) As compared to the abdominal route, the vaginal route for reconstructive procedures has become increasingly popular since it can be performed in regional or local anesthesia, has low complication rates, and is comparatively cheap.

2.3.3.1 Manchester/Fothergill operation

Originally developed in Manchester 1908 where many hard laboring women in the fabric industry developed pelvic organ prolapse, Donald originally described the technique in 1888. It was subsequently modified by Fothergill and involved dissection of the bladder, amputation of the cervix, suturing of the cardinal ligaments to the anterior cervical stump and closure of the posterior vagina over the opening. A so called ‘complete’ Manchester operation also included an anterior and posterior colporraphy.(17) This operative technique has been used over the past 100 years without much change and for almost all types of prolapse.

2.3.3.2 Anterior colporraphy

(Greek: *Kolpos* - fold or hollow, *Raphe* - a seam on an organ)

Howard Kelly described the anterior colporraphy in 1914 originally as an operation for stress urinary incontinence.(50) It was designed to improve urethral support by periurethral plication sutures. The abdominal Burch colpossuspension, developed in 1961 which involves attachment of the periurethral fascia at the level of the bladder neck to the iliopectineal ligament (Cooper’s ligament) has the same objective.(51)

Since then, however, tension free tape procedures have become gold standard in stress urinary incontinence surgery. The anterior colporraphy remains in use but primarily for repair of anterior vaginal wall prolapse.

Anterior colporraphy involves a transvaginal incision of the anterior vaginal wall and dissecting the bulging bladder off the cervix. The bladder is pushed cranially (and sometimes invaginated with a purse string suture) and the pubocervical fascia is adapted in the midline after which the vaginal epithelium is closed. Sometimes excess vaginal mucosa is removed. If defects in the fascia are identified, site specific repair can be performed (specific suturing of identified defects) and if lateral detachments are identified, lateral defect repair can be performed where the endopelvic fascia is reattached to the arcus tendineous fascia pelvis. This procedure is comparatively intricate compared to anterior colporraphy and associated with increased morbidity and poorer results compared to lateral repair using the abdominal route.(52)

2.3.3.3 Posterior colporraphy

The most commonly used procedure for posterior wall prolapse was described by Francis and Jeffcoate.(53) At posterior colporraphy the posterior vaginal wall is incised, the distal rectum freed from the pararectal/rectovaginal fascia after which the levator ani muscles are plicated over the rectum in the midline and the vaginal mucosa is closed. Prolapse in the upper segment of the posterior wall is often caused by an enterocele whereas a lower segment prolapse often is caused by a rectocele.(39) The distinction between the two can be clinically challenging and often diagnosed in the operating room. Surgical repair of an enterocele involves opening the peritoneum and placing a purse string suture in the parietal peritoneal tissue to obliterate the peritoneal cul de sac. The defect is then supported with a McCall culdoplasty by suturing the sacrouterine ligaments into the midline and finally the vaginal epithelium closed. This operation can also be performed by the abdominal route ad modum Moschowitz.(54) Similarly to suturing site specific defects in the anterior pubocervical fascia, site specific repair can also be performed in the rectovaginal fascia.(55)

2.3.3.4 Perineoraphy

The perineal body is often shortened as a result of obstetrical laceration and may be present in patients with posterior wall prolapse. Perineal reconstruction is therefore often a part of posterior vaginal wall repair. This is usually performed with a simple suturing technique.

2.3.3.5 Colpocleisis

A total or partial (le Fort's) is an obliterative technique whereby the vagina is totally or partially closed off by deepithelialising the anterior and posterior vaginal surface and then adapting and suturing the surfaces together. The procedure is rarely performed today.

2.3.3.6 Colpopexy

In cases of vaginal vault prolapse, sacral colpopexy is often the method of choice. This procedure is performed using either the abdominal route where the vaginal apex is lifted cranially and attached to the sacral promontory (sacrocolpopexy) or using the

vaginal route suturing the apex to the sacrospinous ligament (sacrospinous fixation). Attachment to the sacral promontory is performed by open or laparoscopic approach. Although associated with an increased morbidity when compared to sacrospinous fixation, sacrocolpopexy involves transpositioning a mesh between the vaginal apex and the sacral promontory and provides satisfactory anatomical long-term results.(56) In addition, less commonly used techniques for recreating level I support includes fixation to the iliococcygeus and uterosacral ligaments. The McCall culdoplasty involves suturing uterosacral and cardinal ligaments to the vaginal cuff at the time of hysterectomy or posterior colporraphy.(57)

2.3.4 Outcomes of traditional prolapse surgery

The anatomical outcome after surgery has long been considered a straightforward and objective measure by which surgical success is determined. Recently it has, however, become increasingly apparent that vaginal topography postoperatively does not adequately correlate to persistent prolapse symptoms or quality of life.(58) It has therefore been suggested that compound measures which include anatomical results, as well as, subjective symptom scores should be used to describe surgical outcomes in pelvic organ prolapse surgery.(58) There is also an inherent problem in comparing outcomes between different procedures because of the multitude of different surgical techniques in use, the lack of standardization of procedures, concomitant procedures performed at the time of prolapse repair, and the diverse subjective outcome measures.

The definitions of success and failures vary between studies although recently many investigators have used POP-Q stage 0 and I to define postoperative success and stage II or more as failures. Anatomical results for traditional techniques, especially anterior repair, show up to 50% anatomical failures in some reports.(24, 59) Choosing the wrong procedure due to misdiagnosis of the prolapse may of course affect outcomes negatively, for example not addressing an apical defect at the time of anterior vaginal wall prolapse (cystocele) repair. For posterior prolapse, the anatomic success rates are higher than for anterior repair (80-90%) and the midline plication technique has shown superior results as compared to site-specific repair or transanal approach.(60)

In general, vaginal prolapse procedures are associated with low complication rates and are often performed in day surgical settings in regional or even local anesthesia. Major perioperative complications are uncommon but pelvic organ injury, bleeding and hematomas may occur. Minor post operative complications include urinary retention and urinary tract infections (Table 4). Late complications such as de novo stress urinary incontinence have been noted in up to 15% of all prolapse operations.(52) Dyspareunia after posterior repair is a known complication primarily when levator ani plication is performed,(61, 62) and has resulted in a shift towards simple fascial plication.

2.4 IMPLANTS AND MESH

The unsatisfactory recurrence rates associated with traditional pelvic organ prolapse repair have led to the introduction of implants (grafts or mesh) to provide weak or damaged tissues with tensile strength and mechanical support. The introduction of mesh in inguinal hernia surgery has lowered recurrence rates by 50% and mesh augmentation has evolved into the standard care for inguinal herniorraphy.(63) The ambition to identify the ideal graft for urogynecological surgery is a paramount yet

intricate goal, not only in terms of biological tolerance but also in practical and economic aspects.

2.4.1 History

The use of implants in vaginal surgery traces back to the early 20th century when F.H. William in 1904 introduced an operation for the reduction of uterine prolapse by using kangaroo tendon as a purse-string through both broad ligaments. Human fascia lata transplants were used for the treatment of genital prolapse in 1914 and in 1938 fascia lata from ox was used for reconstruction of the round ligaments.(43) In 1941 ribbon catgut was used for suspension of uterine prolapse. Aldridge introduced the fascial sling for urethral support in 1942, and in the same year homologous fascia lata was used for vaginal surgery. Permanent suture materials was first used in 1959 and in 1964 Ferguson was the first to introduce Marlex mesh.(43) Numerous biomaterials have been used since then, mainly for incontinence surgery and vaginal vault suspension.

2.4.2 Implant subgroups

The ideal properties of mesh includes a lack of a foreign body reaction, integration with the host tissues, persistent mechanical properties and long term support to the target tissues. In addition it needs to be chemically inert, non-carcinogenic, non-allergenic, and easily manufactured in sterile and affordable conditions. Host-vs.-implant reactions are influenced by the mesh pore size since it must allow for the invasion of fibroblasts and blood vessels for incorporation and integration with host tissue, as well as, permitting macrophages (10-20 μm in diameter) to pass in order not to compromise antimicrobial defenses. Synthetic meshes are categorized into four subgroups (type I-IV) according to the weave and interstitial pore size,(64) as in Table 3.

Table 3. Classification of synthetic mesh.

Absorbable	Polyglactin 910 (Vicryl) Polyglycolic acid		
Permanent	Monofilament (macroporous >75μm pores)	**Type I** polypropylene, polyvinylidene, fuoride	Marlex Prolene TVT Monarc Gynemesh Trelex
	Multifilament (macro and microporous with <10μm pores)	**Type II** Microporous Polytetra-fluoroethylene	GoreTex
		Type III Macroporous	Teflon Mersilene Dacron IVS
	Submicronic pore size (<1μm)	**Type IV** Silicone, silicone-coated	Rarely used in gyne-cological surgery
Mixed	e.g., Absorbable + non absorbable mesh	Polypropylene + polyglactin 910= type III	Vypro

Synthetic mesh has several potential advantages compared to biological grafts. They are readily available and do not require harvesting. Many synthetic compounds are versatile and can be produced with different weaves or knits and can be designed to have differing tensile strengths, elasticity, and weight properties. Absorbable meshes promote fibroblast activity and because of degradation (within 30-90 days) do not cause prolonged inflammatory reactions or infections. These beneficial traits of absorbables at the same time suggest a limited long term support. Mesh weight is considered to influence the immune response and light weight mesh is generally considered advantageous.(65) Mesh weights vary between light weight mixed mesh e.g. Vypro weighing 50g/m^2 to 96g/m^2 for plain polypropylene mesh such as Gynemesh. The pore size varies between different products from the 700µm Prolene mesh to the mixed mesh Vypro with pores of 2400µm.(8) The elastic limits and tensile strength of permanent synthetic mesh greatly exceed the biologically possible stress which may occur from raised abdominal pressure.(7) Thus, macroporosity of polypropylene monofilament mesh does not compromise the required durability and may contribute to the low rates of mesh complication when used for the tension-free vaginal tape procedure (TVT).(6)

In both urogynecological surgery and abdominal hernia surgery, the use of and experimentation with mesh over many years has resulted in evidence supporting today's preference of synthetic type I mesh over other mesh types. When used for the TVT procedure, macroporous, monofilament, polypropylene mesh has shown advantageous properties as compared with other synthetic biomaterials.(66) As a result, polypropylene mesh has become the most commonly marketed biomaterial also for use in pelvic organ prolapse surgery. Increasing the surface size and adding points of fixation may, however, alter the biomechanical characteristics of the mesh. The favourable outcomes associated with the use of polypropylene mesh for the TVT procedure can therefore not be assumed valid for other areas of pelvic surgery. Due to the lack of clinical safety and efficacy data, the adoption of polypropylene mesh for pelvic organ prolapse surgery remains a source of controversy.(13)

2.4.3 Mesh surgical techniques

The shape of mesh used to reinforce the prolapsed vaginal tissues is either self tailored to the required size with or without mesh arms, or determined by pre-fabricated mesh shapes from the manufacturer. In a further development of these implants it has been suggested that biomaterials need to be anchored in tissues outside the afflicted area to provide the intended pelvic floor support. This has given rise to standardized trocar guided mesh kits with extension arms extending from the central part of the mesh to either the arcus tendineus fascia pelvis (anterior compartment) or the sacrospinous ligaments (posterior compartment).

The transvaginal mesh kit used in the present thesis (Prolift®, Gynecare, Somerville, NJ) was developed by French gynecologists and uses a polypropylene Type I mesh. The compartment specific surgical procedures have previously been described in detail,(8) but are outlined below. The uniformly sized and shaped polypropylene mesh arms are passed through the arcus tendineus fascia pelvis using four metal trocars in the anterior vaginal compartment (Figure 4a). In the posterior compartment, the mesh is placed through a transgluteal approach, and the two extension arms are fixated to the sacrospinous ligament (Figure 4b).

Figure 4a. Anterior trocar guided transvaginal mesh.

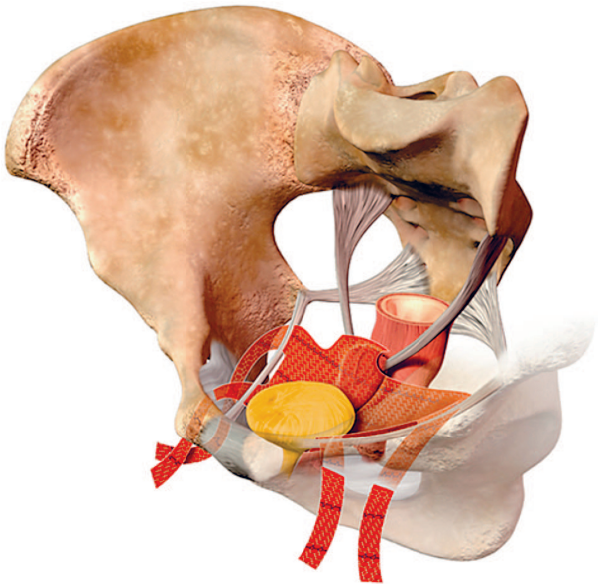
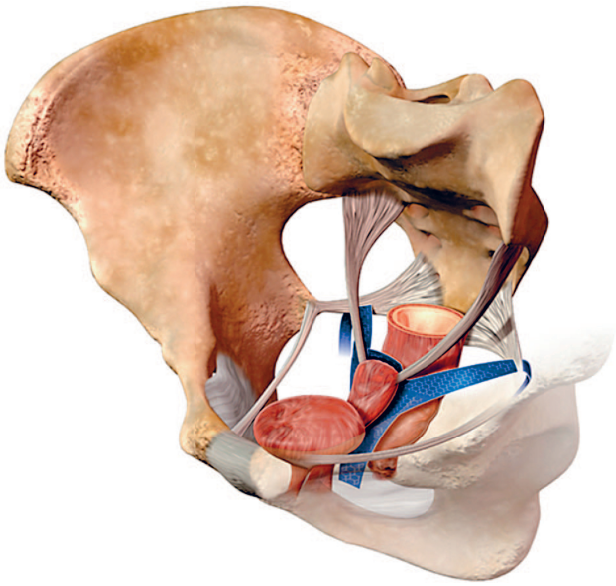


Figure 4b. Posterior trocar guided transvaginal mesh.



Anterior mesh (in red) in final position with extension arms passed through the obturator foramen bilaterally and posterior mesh (in blue) in final position with two extension arms fixated to the sacrospinous ligaments through a transgluteal approach. Copyright ETHICON, Inc. Reproduced with permission.

2.4.4 Vaginal histopathology and immune response

Use of biomaterials in humans results in a host-vs.-implant response caused by an activation of the innate immune system. This involves an activation of macrophages, phagocytes and complement factors. Later, and especially if microbes or proteins persist within the implant, the adaptive immune system also becomes activated causing a proliferation of lymphocytes. In chronic host-vs.-implant reactions, foreign body giant cells can be found. Assessments of the histopathologic response to implants is an important step in recognizing potential detrimental inflammatory reactions and in vivo mesh tolerance.(6) It is likely that larger mesh induces a greater immune response than small mesh used for incontinence surgery and data from the latter cannot be extrapolated to the former.(65)

2.4.5 Success rates and complications of surgical implants

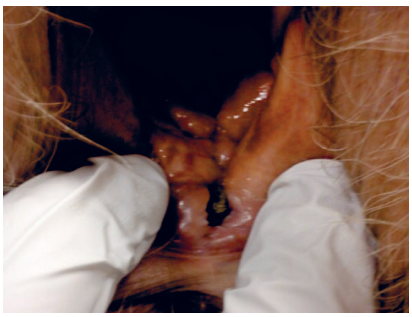
The International Urogynecological Association (IUGA) and ICS have recently published a report on the terminology and classification of mesh related complications in female pelvic floor surgery. The aim is to allow future data comparisons and a possible application is to provide a basis for a registry.(67) It is recommended that terms with greater physical specificity and clarity be used, for example the generic term "erosion" should be avoided and the term *exposure* used instead. The system classifies exposures and other complications according to category, time and site with explanations or subclassifications regarding general description, patient symptoms and infections.

Similar to traditional surgery there are a wide variety of mesh procedures described for pelvic organ prolapse repair and patients often undergo concomitant procedures, making comparisons and definitive conclusions difficult. Case series and prospective cohort studies greatly outnumber randomized trials in the literature.(52) Follow-up times are limited to 1-3 years postoperatively and although systematic reviews show improved anatomical outcomes when using synthetic mesh for anterior repair as compared to traditional surgery, longer follow-up and multiple center data is needed.(68) Observational studies using the Prolift® mesh kit show anatomical success rates ranging from 92-99%, visceral injury in 1-6.6%, de novo SUI in 4.8–24.3% and mesh exposure rates ranging from 2–12%.(69) These figures are similar to recent randomized controlled studies showing higher success rates for mesh as compared to traditional methods.

2.4.5.1 Exposures

Mesh exposures are of major concern in mesh surgery as illustrated by the FDA's notifications in 2008 and 2011.(70) Exposures can occur at any time after surgery but are usually seen within the first year,(71) when the vaginal mucosa covering the mesh becomes thinned eventually exposing the mesh. This may result in vaginal discharge, bleeding, pain and discomfort. Exposures usually arise in the vaginal walls but can also be seen in the bladder or rectum and are visualized on vaginal examination, cystoscopy or rectosigmoidoscopy. Suggested risk factors are concomitant hysterectomy, smoking, increased BMI and age, as well as, an inverted T-incision or proximity to the vaginal scar.(71-74) Minor exposures often heal after local antibiotic or estrogen treatment, whereas larger exposures may need partial or total mesh excision and in rare cases extensive repeated surgery.

Figure 5. Mesh exposure after posterior mesh repair.



2.4.5.2 Lower urinary tract dysfunction

Iatrogenic elevation and straightening of the urethra during pelvic organ prolapse surgery is thought to negatively affect urethral closing pressure and increase the risk of de novo SUI. It is a common notion that the use of mesh increases this effect and the risk of de novo SUI may be greater for mesh than for traditional repair.(75-77) For obstructive urinary tract symptoms anterior repair with mesh have relieved symptoms,(78) whereas others have shown increased detrusor overactivity after the use of mesh.(79)

2.4.5.3 Sexual dysfunction and pain.

A major concern associated with the use of synthetic non absorbable mesh for reconstructive pelvic floor surgery is the risk for adverse effects on sexual function including dyspareunia. De Tayrac observed a 13% rate of de novo dyspareunia after the use of mesh for prolapse repair, although some patients in this study actually reported an improved sexual function.(80) Studies using absorbable mesh or grafts suggest that postoperative dyspareunia is less common,(81) although concerns for unsatisfying durability of degradable implants have demoted their use in prolapse surgery. Evidence regarding dyspareunia in traditional prolapse surgery is conflicting, with some trials showing improvements,(82) whereas traditional posterior prolapse repair has shown dyspareunia in up to one third of patients.(61)

After vaginal wall prolapse surgery postoperative dyspareunia may arise as a combination of disturbed nerve and blood supply to the vaginal wall impairing sexual arousal and lubrication. Overcorrection of the vaginal axis and tautness of the mesh may compromise vaginal elasticity, give rise to vaginal tension, and prevent swelling of the vagina at sexual arousal. The pain caused by tautness can also be experienced outside of sexual intercourse as focal tenderness especially over the mesh arms and is often considered to be the result of mesh contraction.(83) Sexual function is complex and comprises not only the physical ability to have intercourse but also psychological aspects like self esteem and self image, as well as, partner ability. The frequency of sexual dysfunction in women with urogynecological disorders is high and there is a paucity of data on how synthetic mesh for pelvic organ prolapse influences the various domains of female sexual function.(84)

Long term buttock, groin or pelvic pain can affect women after both traditional prolapse repairs, as well as, after mesh procedures with rates varying between 0-18.3%.(85) Reasons for persistent pelvic pain may involve nerve damage, mesh tensions, and mesh contraction.

Table 4. Review of outcomes in randomized controlled trials on the use of transvaginal mesh for pelvic organ prolapse.

				Perioperative complications				Complications during follow up		
Author year	**Follow up**	**Method**	**Ana-tomic success rate**	**Visceral injury**	**Hemorrhage**	**Urinary retention**	**UTI**	**Exposures**	**De novo dyspareu-nia**	**De novo SUI**
Nguyen 2008 *(A)*	1 year	Mesh	33/38 (87%)	none	1 blood-transfusion	2/37 (5.4%)	4/37 (10.8%)	2/37 (5.4%)	2/23 (8.7%)	NR
		Traditional repair	21/38 (55%)	none	1 blood-transfusion	2/38 (5.3%)	7/38 (18.4%)	NA	4/26 (15.4%)	NR
Carey M 2009 *(A+P)*	1 year	Mesh	51/63 (81%)	-	"significant blood loss"	NR	NR	4/71 (5.6%)	5/30 (16.7%)	NR
		Traditional repair	40/61 (65.6%)	1 bladder and 1 bowel perforation	-	NR	NR	NA	5/33 (15.2%)	NR
Altman 2010 *(A)*	1 year	Mesh	153/186 (82.3%)	7 bladder perforations	Blood loss 84.7ml	3/200 (1.5%)	12/200 (6%)	21/183 (11.5%)†	(7.3%)‡	22/179 (12.3%)
		Traditional repair	87/183 (47.5%)	1 bladder perforation	Blood loss 35.4ml	2/189 (1.1%)	8/189 (4.2%)	NA	(2%)‡	11/176 (6.3%)
Nieminen 2010 *(A)*	3 years	Mesh §	14/105 (87%)	1 bladder perforation*	2 blood-transfusions*	11%‡	NR	20/95 (19%)	4‡**	7%‡
		Traditional repair	40/97 (59%)	-	-	8.3%‡	NR	NA	8‡**	5%‡
Withagen 2011 *(A+P)*	1 year	Mesh	75/83 (90.4%)	2 bladder perforations	Blood loss 100ml	15/93 (16%)	NR	14/83 (16.9%)	3/37 (8%)	6/50 (12%)
		Traditional repair	46/84 (54.8%)	-	Blood loss 100ml	5/97 (5%)	NR	NA	3/29 (10%)	6/53 (11%)

A= Anterior repair, *P*= Posterior repair. NR = not reported. *Reported by Hiltunen 08. † figures from supplementary analysis.

‡No numerator / denominator available. § Mesh placed over fibromuscular layer. ** Described as "operation had caused some inconvenience at intercourse"

3 AIMS

The aim of this thesis is to study clinical and histological aspects on the use of a trocar guided transvaginal mesh kit for pelvic organ prolapse repair.

The specific aims were to:

1. Investigate the subjective and objective clinical outcomes one year after pelvic organ prolapse repair using a trocar-guided mesh kit. (Paper I)

2. Prospectively evaluate sexual outcomes one year after pelvic organ prolapse repair using a trocar-guided mesh kit. (Paper II)

3. Examine the histological inflammatory response one year after transvaginal pelvic organ prolapse repair using mesh. (Paper III)

4. Assess potential risk factors associated with the development of exposures one year after transvaginal pelvic organ prolapse repair using mesh. (Paper IV)

4 PATIENTS

All patients included in the four studies attended one of the clinics taking part in the Nordic Transvaginal Mesh (TVM) group. The Nordic TVM group is an independent collaboration between clinicians in Sweden, Norway, Denmark and Finland with the aim of performing multicenter studies in pelvic reconstructive surgery. Patients included in paper I and II in the present thesis were included at 26 different clinics in the Nordic countries. The patients in paper III was a subgroup of patients only from the Department of Obstetrics and Gynecology at Danderyd Hospital. In paper IV data was combined from two multicenter trials including 52 clinics and limited to patients with anterior wall prolapse. All studies were approved by the Research Ethical Review Board in Stockholm and the appropriate IRB committees in all participating countries.

4.1 PAPER I

In this prospective cohort study 261 patients with symptomatic pelvic organ prolapse were included at 26 centers in the Nordic countries between June 2006 and March 2007 (see Appendix 14.3 for participating centers). Nine women were excluded from the study due to missing information. Mean age at surgery was 66.3 (± 9.4 SD) years and median parity was 2 (range 0-7). Approximately half of the patients (50.8%) had undergone previous traditional prolapse surgery. Almost one tenth of the women were smokers (9.5%) and 88.9% were postmenopausal; 62.3% used local or systemic hormone replacement therapy. Almost half of the women underwent anterior repair (48.0%) whereas 27% underwent posterior repair and 25% anterior and posterior repair using either two separate meshes or a combined anterior-posterior mesh.

4.2 PAPER II

Sexually active women participating in a prospective cohort study between June 2006 and March 2007 were included in this auxiliary study. A total of 105 women were included in 26 centers (see Appendix 14.3 for participating centers). Their mean age at surgery was 61.5 (±7.6 SD) years which was younger than the sexually inactive group (mean age 69.0 ±4.2 SD years). Median parity was 2 (range 1-6), mean BMI 26.8 (±4.3 SD) kg/m^2 and 89% were postmenopausal. 41% had undergone previous prolapse surgery. The proportion of women undergoing anterior prolapse repair was 44%, posterior 25% and combined anterior and posterior repair 31%. Aside from age, baseline characteristics were similar between the sexually active and inactive group.

4.3 PAPER III

Ten women with pelvic organ prolapse at the Department of Obstetrics and Gynecology at Danderyd Hospital were asked to undergo vaginal punch biopsy sampling. We also included 8 control subjects i.e. women undergoing vaginal surgery at the same clinic for reasons other than pelvic floor dysfunction. Exclusion criteria for patients and controls alike included pelvic organ cancer, severe rheumatic disease, systemic steroid treatment or connective tissue disorders.

4.3.1 Patients

The mean age for the 10 patients was 67.1 (±7.5 SD) years, median parity was 2 (range 1-4), and mean BMI was 26.5 (±4.8 SD) kg/m^2. All of the patients were postmenopausal, 7 used local or systemic hormone replacement therapy and there were no smokers. 4 of the women underwent anterior prolapse repair, 2 posterior repair and 4 combined anterior and posterior repair.

4.3.2 Controls

For the 8 controls mean age was 42 (±13.0 SD) years, median parity was 2 (range 0-2), two were postmenopausal and none used local or systemic hormone replacement therapy. Mean BMI was 23.6 (±4.0 SD) kg/m^2 and none were smokers.

4.4 PAPER IV

In this study, all patients undergoing surgical repair of anterior vaginal wall prolapse with mesh in a prospective cohort study and a randomized controlled trial were included (see Appendix 14.3 for participating centers). Mean age at surgery was 65.3 (± 9.6 SD) years, mean BMI was 26.5 (±3.8 SD) kg/m^2 and median parity was 2 (range 0-7). More than one third of the patients (35.6%) had undergone previous corrective prolapse surgery. There were 37 smokers (10.5%) and the number of women suffering from somatic inflammatory disease was 12 (3.4%) of which rheumatic disease was the predominant diagnosis. Most women (82.7%) were postmenopausal and 69.4% used local or systemic hormone replacement therapy.

5 METHODS

5.1 STUDY DESIGN

In this segment the study design for papers I-IV included in the present thesis are outlined.

5.1.1 Paper I

A multicenter, prospective, cohort study evaluating subjective and objective clinical outcomes among women undergoing trocar guided transvaginal mesh surgery for pelvic organ prolapse. Clinical examinations and subjective symptom assessments were performed before surgery, at two months and one year postoperatively. Symptom assessments were performed using validated and condition specific questionnaires (described in section 6.3). Trial protocols were submitted to the clinical research unit at the Department of Obstetrics and Gynecology, Danderyd Hospital, Stockholm, Sweden, and only the principal investigators had access to the data. All gynecologists participating in the trial were experienced pelvic surgeons and had pretrial, supervised, hands-on training in operating room sessions. The transvaginal mesh manufacturing company had no influence over study aim, design, execution or analysis and interpretation of data.

5.1.2 Paper II

The focus of this study was to assess sexual function in women participating in a multicenter, prospective, cohort study. Clinical examination and symptom assessment using validated and condition specific sexual function questionnaires (section 6.3) were performed prior to surgery and one year after surgery. Only patients sexually active before surgery were included in the analysis.

5.1.3 Paper III

This was a prospective, comparative, histopathological study. Ten women included in the multicenter cohort study (see section 6.1.1.) from Danderyd Hospital were included, as well as, 8 control subjects. Vaginal punch biopsy sampling was performed at baseline and one year postoperatively in patients. In control subjects punch biopsies were obtained only at baseline. Mesh inflammatory response was investigated macro- and microscopically.

5.1.4 Paper IV

In this study we combined patients from two multicenter studies. Data on women having anterior trocar guided transvaginal mesh in a prospective cohort study and a randomized controlled trial were combined and analyzed to identify risk factors for clinical mesh complications. Both studies used the same surgical mesh kit for anterior prolapse repair (Gynecare Prolift® Anterior Pelvic Floor Repair System kit, Ethicon) and the study protocol was near identical for both studies with regard to inclusion and exclusion criteria, as well as pre- and postoperative care. The studies differed mainly by the randomized design in one study and that the prospective cohort study allowed concomitant surgery at the time of mesh kit repair. The present combined analysis of the two studies was limited to women who underwent anterior prolapse mesh kit repair

and did not include posterior or total mesh kit repair in the cohort study, or women having colporraphy (without mesh) in the randomized trial.

5.2 CLINICAL EXAMINATION

A clinical examination was performed at baseline, two months and one year. Objective outcome measures were anatomical prolapse stage and macroscopic signs of vaginal inflammation. POP-Q quantification was performed for prolapse staging and assessment of inflammatory status was performed using a macroscopic inflammatory scale.

5.2.1 POP-Q

Before undergoing pelvic organ prolapse surgery all patients underwent a gynecological examination in the supine position, using the POP-Q system. Methods, definitions, and descriptions conformed to the standards recommended by the ICS.(40) Postoperative prolapse stage 0–I was considered anatomical cure. POP-Q measurements and staging at pre- and postoperative examinations were recorded in a separate protocol.

5.2.2 Macroscopic inflammatory scale

At the time of designing the study, no internationally accepted standard terminology or classification system was available to assess vaginal epithelial inflammation after pelvic organ prolapse surgery. Therefore a scoring system devised by Zdichavsky was used.(86) The terminology in paper IV, and throughout this thesis, has been changed to reflect the recommended terminology but the classification system could not be implemented retrospectively. The terms “erosion” and “rejection” have been replaced by *exposure* and *extrusion* respectively. At vaginal examination, granuloma, (erosion) exposure, necrosis, infection and (rejection) extrusion were graded according to a 5 point ordinal scale (0= none, 1= mild, 2= moderate, 3= pronounced, 4= severe). The scale is not formally validated for use in urogynecological surgery but has shown consistency with histopathologic assessments in a previous study assessing the use of biomaterials in pelvic floor surgery.(87)

5.3 QUESTIONNAIRES

In paper I and II subjective outcomes were measured using symptom specific questionnaires assessing the impact of pelvic organ prolapse on urinary symptoms, quality of life and sexual function.

5.3.1 UDI-6

The Urinary Distress Inventory (UDI) used in paper I was first developed in 1994 by Shumaker et al specific to symptoms associated with lower urinary tract dysfunction and genital prolapse.(88) The UDI focuses on lower urinary tract symptom distress and contains 19 items in its original form. The short form was developed and validated in 1995,(89) and it is this form with 6 items that we used in the present studies. The UDI contains three subscales of lower urinary tract symptoms: Stress Symptoms, Obstructive/ Discomfort, and Irritative symptoms. There are two questions for each subscale in the short form. The item responses are assigned values of 0 for ‘not at all’, 1

for ‘slightly’, 2 for ‘moderately’, and 3 for ‘greatly’, hence the maximum score is 18. Scores are calculated in a simple additive fashion and for missing responses an average value is calculated and used, though if more than two responses are missing, the score should not be calculated. Higher scores indicate worse symptoms.

5.3.2 IIQ-7

The Incontinence Impact Questionnaire (IIQ) long and short forms were developed in parallel with the UDI. The 7-item short form used in the present studies is a quality of life impact assessment instrument and was constructed with a similar scoring system as the UDI. The IIQ is divided into 4 subscales; Physical Activity (2 items), Travel (2 items), Social/Relationships (1 item), and Emotional Health (2 items). Scores are calculated in the same way as the UDI. The maximum score for the IIQ-7 is 21 and higher scores indicate worse quality of life.

5.3.3 PISQ-12

The long form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire developed in 2001 is a 31-item questionnaire.(90) It was condensed into a 12-item short form and validated in 2003,(91) in order to achieve wider applicability in clinical and research settings. It assesses sexual function in women with pelvic organ prolapse or urinary incontinence and enables an evaluation of quality of life changes after surgical or medical interventions. Responses are graded on a 5-point ordinal Likert scale where 0 is ‘never’, 1 is ‘seldom’, 2 is ‘sometimes’, 3 is ‘usually’ and 4 is ‘always’. The questionnaire is divided into 3 subscales: Behavioral/ Emotive (4 items), Physical (5 items) and Partner Related (3 items). Scoring is performed in a simple additive fashion and the maximum score is 48.

5.4 VAGINAL PUNCH BIOPSY SAMPLING

Punch biopsy sampling in order to evaluate histological inflammatory response to vaginal mesh surgery was performed in paper III. Sampling was performed at the time of surgery in patients and controls but postoperative sampling at one year follow-up was only performed in patients. At the one year follow up patients received local anesthesia consisting of up to 5ml 0.25% Marcain® + epinephrine at the biopsy site. Biopsies were taken using a 6 mm wide and 10 mm deep punch biopsy instrument in the vaginal wall. The placing of the biopsy was in either the anterior or posterior vaginal wall in the same manner both pre- and postoperatively. By palpating the vaginal walls at the one year follow-up it was possible to feel the mesh beneath the mucosa and the biopsy was thereby taken in as close proximity as possible to the mesh-tissue interface. For posterior biopsies the punch biopsy was directed diagonally downwards in order to avoid the rectum or diagonally upwards for anterior biopsies in order to avoid the urethra and bladder. Care was taken so as not to engage the mesh in the biopsy.

5.5 HISTOLOGICAL ANALYSIS

After sampling, biopsies were immediately immersed in a 4% neutral buffered formaldehyde solution after which they were transported to the pathology lab at Astra Zeneca R&D laboratories, Södertälje, Sweden, where they underwent dehydration and

embedding in paraffin. They were cut with a microtome into 5 µm sections and two specimens were prepared for each biopsy. The first was stained with hematoxylin and eosin and the other left unstained. The following parameters were evaluated using the stained specimens:

- Total cell content in the subepithelial tissue
- Epithelial thickness
- Manual cell counts
- Semiquantitative grading of inflammation, vasculitis and collagen density

Using the unstained specimen the following was analyzed:

- Elastin area fraction

All measurements were performed together with a single pathologist blinded to clinical outcome. A computer assisted morphometric analysis was performed for total cell content and epithelial thickness measurements using a Sony® DXC-9100P 3-chip charge coupled device color camera mounted on an Axioplan™ 2 light microscope to capture images which were then analyzed using the MicroGOP 2000s image analysis software (Context Vision AB, Linköping, Sweden) installed in a SUN SPARCstation™ 20 computer workstation.

Figure 6. Axioplan™ 2 light microscope.

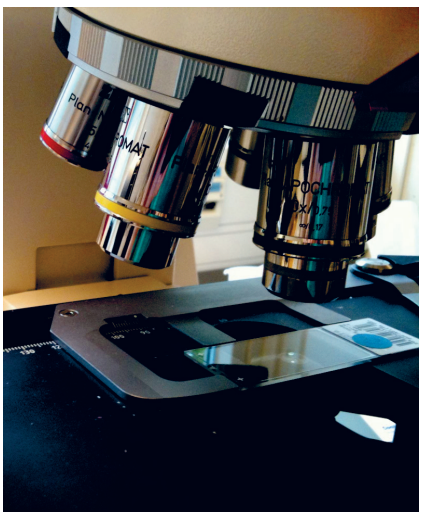
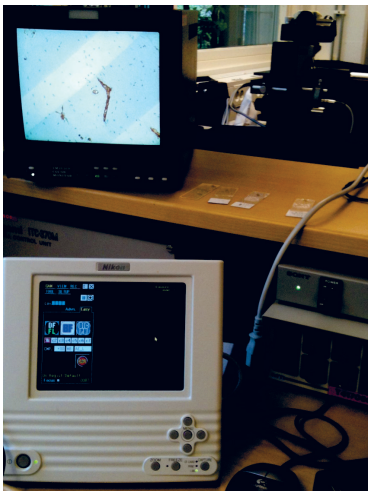


Figure 7. SUN SPARC work station.



S*ubepithelial total cell content*
The captured image was processed and an unbiased counting area frame of 50 000 μm^2 was superimposed on the image to calculate the numerical density of cells per μm^2. Three such measurements were performed on each specimen.

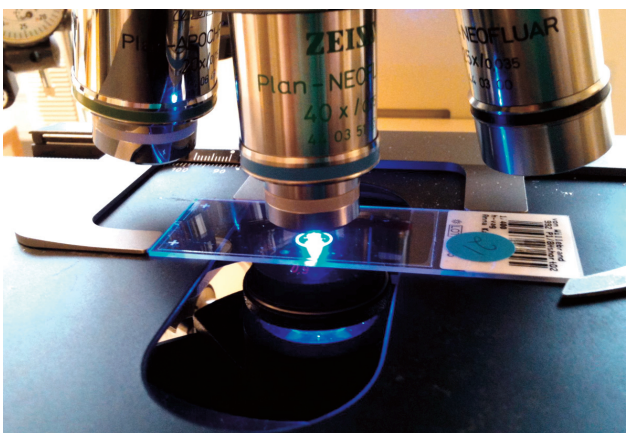
Epithelial thickness
A binary epithelial profile of the images was created using the computer workstation and epithelial height (distance from basement layer to surface), distance from the top of the dermal papillae to the surface and distance between dermal papillae tops was measured.(92)

Manual cell counts
Using a light microscope and 100x oil immersion objective, specimens were examined and 200 cells counted; the cell counts for fibroblasts, macrophages, monocytes, granulocytes, lymphocytes, plasma cells and mast cells were registered.

Semiquantitative grading
Using the same microscope as above, overall inflammation and vasculitis was graded from 0 to 4 (0= none, 1= mild, 2= moderate, 3= pronounced, 4= severe) and collagen density graded as loose, fairly dense, moderately dense or very dense.

Elastin area fraction
Elastic fibers have autofluorescent properties; therefore they were analyzed using a Neofluor optical lens (Carl Zeiss, Jena, Germany) and fluorescent light in the same microscope, as above. Using the 40x objective, specimens were illuminated with ultraviolet light (filter range 450 to 500nm) to detect autofluorescence signals from the elastic fibers. A reference area of 54,162 μm^2 was used for all captured images and each image consisted of 512 x 512 pixels. Area fraction was then analyzed using image analysis software as a percentage of the total tissue area; the measurement was performed three times for each specimen.(93)

Figure 8. Neofluor optical lens (Carl Zeiss, Jena, Germany) with fluorescent light.



6 STATISTICAL ANALYSES

All analyses were performed using Statistica (StatSoft, Inc., Tulsa, OK) and PASW (IBM, SPSS Inc; Chicago, IL, U.S.A) software and for all studies, $p<0.05$ was considered significant.

6.1 PAPER I

The IIQ-7 and UDI-6 questionnaire scores were calculated in a simple additive fashion (94). For dependent samples, comparisons on ordinal data between baseline and the 2-month and 1-year assessment were performed using the nonparametric Wilcoxon signed rank test. A post hoc power analysis was performed based on the observed rates of anatomic cure (85%) and aiming at 80% power at a 95% confidence interval (i.e. β=20% and α=5%). A required total sample size of 196 was calculated which indicates that the number of patients in our study was adequate.

6.2 PAPER II

The summated PISQ-12 scores were calculated in a simple additive fashion where higher scores reflected better sexual functioning.(91) Comparisons between baseline, 2 months and 1 year were performed for dependent samples using Wilcoxon signed rank test. The independent variables age, body mass index, current cigarette smoking, menopausal status, childbirths, anatomical failure, mesh exposures and concurrent surgery were tried in a forward multivariable logistic regression model in order to identify risk factors for a poor sexual function score. A post hoc power analysis aiming at 80% power at a 95% confidence interval (i.e. β=20% and α=5%) using a comparison of two observed means (mean PISQ score at baseline (15.5) and 1 year (11.7)) resulted in a sample size of 61 in each group. Preoperative scores could be calculated for 93 patients and postoperative scores for 69 indicating an adequate sample size.

6.3 PAPER III

Comparisons of proportions were performed using the chi-square test. For data comparing baseline and one year, dependent samples were analyzed using the nonparametric Wilcoxon signed rank test. For independent samples comparisons were performed using the nonparametric Mann-Whitney U test.

6.4 PAPER IV

Comparisons on data between baseline and the two month and one year assessments were performed using the non-parametric Wilcoxon signed rank test for dependent samples, the Mann-Whitney U test for independent samples, and χ^2 test for cross tabulation. Dichotomized variables assumed to be risk factors for the dependent variable (mesh exposure at one year) were chosen a priori clinical relevance and a literature review and analyzed using stratification and logistic regression. Multiple regression analysis was performed in both forward and backward stepwise removal of variables so as not to overlook any possible non significant variables in the univariate analysis.

7 RESULTS

7.1 PAPER I

7.1.1 Patient characteristics

Of the 261 patients included at baseline, 9 were excluded due to missing information and 20 were lost to follow up. 243 (93%) and 232 (89%) attended the 2 month and one year follow-up respectively. For 128 patients (50.8%) mesh surgery was performed as a secondary procedure due to recurrent prolapse. Patient characteristics are shown in Table 5.

7.1.2 Surgical characteristics

Out of 261 patients, 121 (48%) underwent anterior repair, 68 (27%) posterior repair and 63 (25%) underwent combined anterior-posterior repair. Concurrent surgery (usually posterior repair and perineorraphy in patients undergoing anterior repair) was performed in 34 (13%) patients. Serious perioperative complications occurred in 10 (3.8%) patients: 8 bladder- and 1 rectal perforation and one hemorrhage in excess of 1500 ml. Surgical characteristics are shown in Table 6.

7.1.3 Anatomic outcomes

Overall anatomic cure defined as POP-Q stage 0-I postoperatively was observed in 81-87% of patients at 2 months and in 79-86% at one year depending on compartment. The highest cure rates were seen in the posterior compartment. Detailed cure rates, POP-Q stages and measurements are shown in Tables 7 and 8.

Table 5. Patient characteristics

	Anterior repair *(n=121)*	**Posterior repair** *(n=68)*	**Anterior & Posterior Repair** *(n=63)*
Age[a]	66.0 ± 8.4	66.7 ± 10.2	66.3 ± 10.4
Parity[b]	2 (0-5)	2 (0-6)	3 (0-7)
Body Mass Index[a]	27.1 ± 4.2	26.3 ± 4.1	26.1 ± 3.6
Educational level[c]			
Compulsory school	81 (67)	34 (50)	25 (40)
High school	23 (19)	16 (24)	19 (30)
College/university	15 (12)	13 (19)	12 (19)
Annual income[c]			
€ <10,000.0	22 (18)	12 (18)	10 (16)
€ 10,000.0-30,000.0	77 (64)	25 (37)	24 (38)
€ 30,000.0-40,000.0	5 (4)	12 (18)	5 (8)
€ >40,000.0	2 (2)	4 (6)	1 (2)
Smoker[c]			
Yes	9 (7)	9 (13)	6 (10)
No	111 (92)	58 (85)	54 (86)
Menopausal[c]			
Yes	110 (91)	59 (87)	55 (87)
No	4 (3)	4 (6)	2 (3)
Hormone Replacement Therapy[c]			
Local	49 (40)	22 (32)	21 (33)
Systemic	33 (27)	19 (28)	13 (21)
Somatic diseases[c]			
CVD	52 (43)	26 (38)	34 (54)
Thyroid dysfunction	16 (13)	8 (12)	8 (13)
Asthma	9 (7)	6 (9)	5 (8)
Arthrosis	6 (5)	6 (9)	4 (6)
Diabetes	4 (3)	3 (4)	4 (6)
Previous pelvic surgery[c]			
Hysterectomy	55 (45)	37 (54)	39 (62)
Prolapse	73 (60)	32 (47)	23 (37)
Incontinence	8 (7)	9 (13)	6 (10)
Salpingo-oophorectomy	27 (22)	22 (32)	10 (16)
Other	9 (7)	8 (12)	3 (5)

Numbers not adding up to 100% represent missing values.

[a] Mean ± SD, [b] Median (range), [c] Number of patients (%)

Table 6. Surgical characteristics and adverse events associated with transvaginal mesh repair using the Prolift™ system

	Anterior repair *n=121*	**Posterior repair** *n=68*	**Anterior& posterior** repair *n=63*
Operating time (min)*	59.7 ± 20.2	54.4 ± 18.6	96 ± 36.9
Antibiotic prophylaxis‡	116 (95.9)	66 (97.1)	60 (95.2)
Bleeding (ml)*	103.4 ± 110.2	52.8 ± 55.6	168.5 ± 216.8
Concurrent surgery			
Hysterectomy	3 (2.5)	0 (0)	5 (7.9)
Anterior colporraphy	NA	2 (2.9)	NA
Posterior colporraphy	8 (6.6)	NA	NA
TVT/TVT-O	1 (0.8)	1 (1.5)	1 (1.6)
Sacrospinous fixation	3 (2.5)	0 (0)	0 (0)
Cervix amputation	1 (0.8)	0 (0)	0 (0)
Perineoraphy	6 (5)	6 (8.8)	4 (6.3)
Anesthesia‡			
Local	9 (7.4)	6 (8.8)	2 (3.2)
Epidural	1 (0.8)	2 (2.9)	1 (1.6)
Spinal	69 (57)	45(66.2)	38 (60.3)
General	39 (32.2)	13 (19.1)	17 (27)
Perioperative catheter‡	105 (86.8)	55 (80.1)	58 (92.1)
Postoperative vaginal tamponade‡	89 (73.6)	44 (64.7)	44 (69.8)
Hospital stay (days)†	2 (0-15)	2 (0-7)	2 (0-13)
Complications‡			
Bladder perforation	6 (5)	0 (0)	2 (3.2)
Rectal perforation	0 (0)	0 (0)	1 (1.6)
Urinary tract infection	4 (3.3)	2 (2.9)	3 (4.8)
Bladder retention	11 (9.1)	3 (4.4)	5 (7.9)
Groin/buttock pain	3 (2.5)	1 (1.5)	1 (1.6)
Vaginal hematoma	1 (0.8)	2 (2.9)	2 (3.2)
Cardiovascular disease	6 (5)	2 (2.9)	2 (3.2)

Figures are ‡Number of patients (%), *Mean ± SD and †Median (range)

Variables not adding up to 100% represent missing values

Table 7. Anatomic cure rates

	Anterior repair		**Posterior repair**		**Anterior and posterior repair**	
	2 months	1 year	2 months	1 year	2 months	1 year
Anterior compartment	98/121 (81%)	96/121 (79%)	NA	NA	52/63 (83%)	51/63 (81%)
Posterior compartment	NA	NA	58/68 (85%)	56/68 (82%)	55/63 (87%)	54/63 (86%)

P<0.001 for all (comparisons with baseline)

Table 8. POP-Q measurements

	Anterior repair		**Posterior repair**		**Anterior and posterior repair**	
	Baseline	1 year	Baseline	1 year	Baseline	1 year
Anterior						
Ba	2(-1 to 7)	-2(-4 to 3)	-2(-3 to 1)	-2(-3 to 1)	2(-1 to 8)	-2(-4 to 0)
Stage	II (II to IV)	I (0 to III)	I (0 to II)	I (0 to II)	II (II-IV)	I (0 to II)
Middle						
C	-1(-1 to -9)	-6(-10 to -4)	-3(-9 to 9)	-6(-11 to -4)	2(-10 to 8)	-6(-12 to -4)
Stage	I (0 to II)	I (0 to II)	I (0 to IV)	I (0 to II)	II (0 to IV)	I (0-II)
Posterior						
Bp	-2(-3 to 0)	-2(-3 to 2)	2(-1 to 5)	-3(-3 to 3)	2(-1 to 8)	-3(-3 to 3)
Stage	I (0-II)	I (0-II)	III (II-IV)	I (0-III)	II (II-IV)	I (0-III)

Data are median (range).

7.1.4 Macroscopic inflammatory assessment

All inflammatory measurements increased postoperatively in comparison with baseline (Table 9). Signs of granuloma and extrusion dropped in prevalence after an initial increase, but the number of exposures increased to 26 of 232 cases (11%, 95% CI 7.2–15.3%) 1 year after surgery. There was no increase in mesh-related infections at 1 year compared to baseline. The median severity score was 0 for all measures throughout the study, and most cases of mesh reactions were in the range of mild-to-moderate severity. Although no cases of severe inflammatory reactions were reported, the need to cover or remove exposed mesh during the postoperative period was reported in seven cases (2.8%, 95% CI 0.8 –5.2), five after anterior mesh repair and two after posterior repair. The remaining cases of mesh exposures were all managed conservatively using topical estrogen or antibiotic cream.

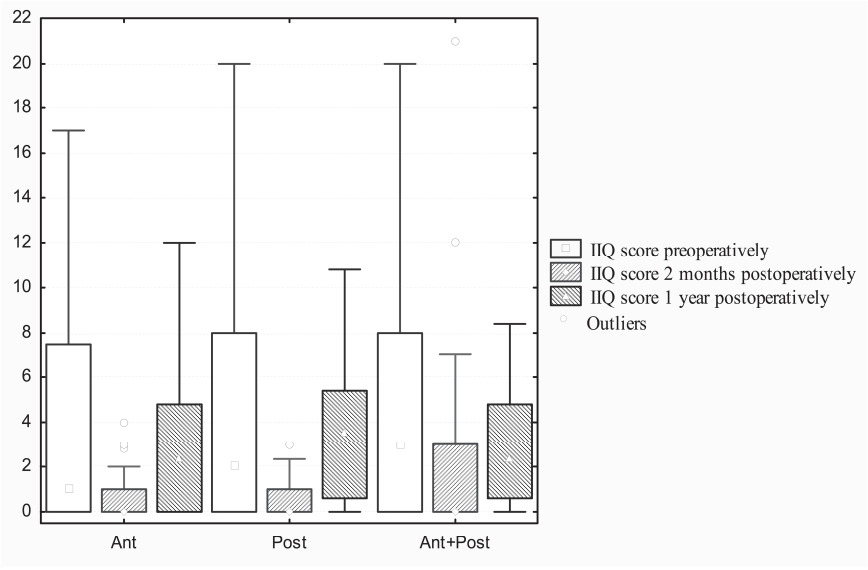
Table 9. Macroscopic assessment of clinical inflammatory reactions to transvaginal mesh.

	Preoperatively N= 252		**2 months** n= 243			**1 year** n= 232		
	No. of cases (%)	Median severity (range)	No. of cases (%)	Median severity (range)	P-value	No. of cases (%)	Median severity (range)	P-value
Total	13 (5)		128 (53)		p< 0.001	65 (28)		p< 0.001
granuloma	3 (1)	0 (0-2)	73 (30)	0 (0-3)	p< 0.001	19 (8)	0 (0-2)	p< 0.001
exposure	6 (2)	0 (0-3)	16 (7)	0 (0-2)	p= 0.02	26 (11)	0 (0-3)	p= 0.001
necrosis	1 (1)	0 (0-1)	11 (5)	0 (0-2)	p= 0.003	12 (5)	0 (0-2)	p= 0.001
infection	3 (1)	0 (0-1)	10 (4)	0 (0-2)	p= 0.04	4 (2)	0 (0-2)	p= 0.62
extrusion	0 (0)	0 (0-2)	18 (7)	0 (0-2)	p< 0.001	4 (2)	0 (0-2)	p= 0.04

7.1.5 Subjective outcomes

There were significant postoperative improvements in IIQ-7 scores in all surgical compartments (Figure 9). Detailed outcomes are presented in Table 10.

Figure 9. IIQ-7 scores in relation to surgical procedure.



Boxplot displaying median scores, interquartile range and non outlier range.

Ant denotes anterior prolapse repair, Post denotes posterior prolapse repair, and Ant+Post denotes combined anterior and posterior prolapse repair.

Table 10. Outcomes of the short-form Incontinence Impact Questionnaire (IIQ-7)

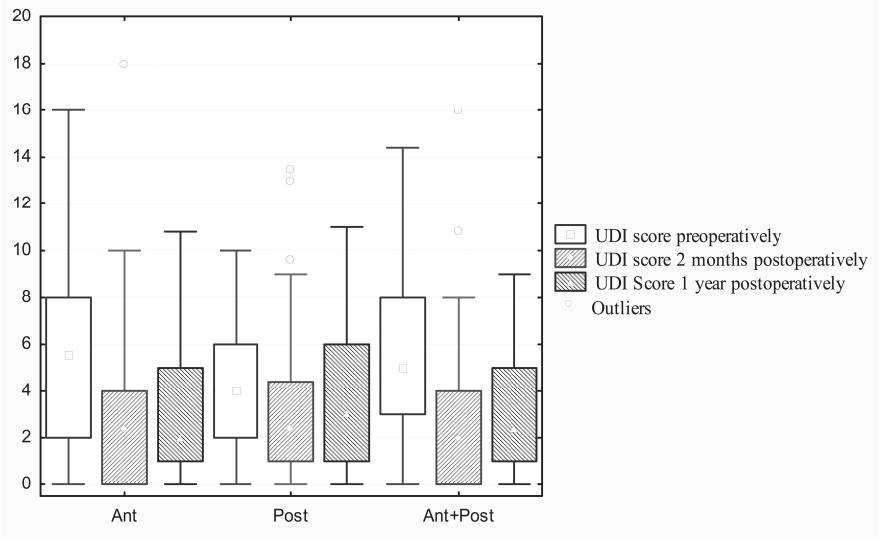
	Anterior repair		**Posterior repair**		**Anterior and Posterior repair**	
	n=121		n=68		n=63	
How does incont affect your:	Preop	1 year	Preop	1 year	Preop	1 year
Household chores		p<0.001		p<0.001		p=0.002
Not at all	76 (63)	92 (76)	43 (63)	55 (81)	36 (57)	49 (78)
Slightly- Mod	34 (28)	12 (10)	17 (25)	6 (13)	21 (33)	8 (13)
Greatly	4 (3)	1 (1)	4 (6)	0 (0)	3 (5)	1 (2)
Physical recreation		p<0.001		p<0.001		p<0.001
Not at all	57 (47)	82 (68)	30 (44)	43 (63)	31 (49)	43 (68)
Slightly- Mod	44 (36)	24 (20)	24 (35)	16 (24)	22 (35)	14 (22)
Greatly	10 (8)	1 (1)	6 (9)	2 (3)	6 (10)	0 (0)
Entertainment activities		p<0.001		p=0.02		p=0.02
Not at all	75 (62)	94 (78)	37 (54)	46 (68)	37 (59)	48 (76)
Slightly- Mod	31 (26)	11 (9)	16 (23)	11 (16)	13 (21)	9 (14)
Greatly	5 (4)	1 (1)	7 (10)	3 (4)	6 (10)	0 (0)
Ability to travel by car/bus >20 min		p=0.002		p=0.05		p<0.001
Not at all	80 (66)	94 (78)	43 (63)	49 (72)	42 (67)	51 (81)
Slightly- Mod	29 (24)	10 (8)	12 (10)	10 (15)	14 (22)	7 (11)
Greatly	5 (4)	0 (0)	6 (9)	0 (0)	4 (6)	0 (0)
Social activities		p<0.001		p=0.02		p=0.002
Not at all	74 (61)	90 (74)	37 (54)	51 (75)	35 (56)	46 (73)
Slightly- Mod	34 (28)	14 (12)	15 (22)	6 (13)	17 (27)	9 (14)
Greatly	5 (4)	0 (0)	5 (7)	3 (4)	6 (10)	1 (2)
Emotional health		p=0.002		p=0.01		p=0.01
Not at all	82 (68)	89 (74)	40 (59)	52 (76)	38 (60)	41 (65)
Slightly- Mod	28 (24)	13 (11)	13 (19)	7 (10)	14 (22)	13 (21)
Greatly	2 (2)	0 (0)	3 (4)	0 (0)	6 (10)	2 (3)
Feeling frustrated		p<0.001		p<0.001		p<0.001
Not at all	69 (57)	91 (75)	30 (44)	48 (71)	30 (48)	45 (71)
Slightly- Mod	37 (31)	13 (11)	21 (31)	11 (16)	17 (27)	12 (19)
Greatly	5 (4)	0 (0)	5 (7)	0 (0)	9 (14)	0 (0)
Summated IIQ-7 score Mean (SD)	3.9 (±4.9)	p=0.1 2.8 (±2.9)	4.3 (±5.4)	p=0.05 3.3 (±2.7)	5.0 (±6.0)	p=0.03 2.8 (±2.5)

Figures are frequency (%). Mod (Moderately), Incont (Incontinence)

Statistical comparison between preoperative values and 1-year follow-up using the Wilcoxon signed rank test.

UDI-6 scores also improved in all surgical compartments postoperatively as seen in Figure 10. Detailed outcomes are shown in Table 11. The five participants (2%) who underwent surgery for stress urinary incontinence during the follow-up period were not included in the final UDI-6 analysis.

Figure 10. UDI-6 scores in relation to surgical procedure.



Boxplot displaying median scores, interquartile range and non outlier range.
Ant denotes anterior prolapse repair, Post denotes posterior prolapse repair, and Ant+Post denotes combined anterior and posterior prolapse repair.

Table 11. Outcomes of the short-form Urinary Distress Inventory (UDI-6).

	Anterior repair		**Posterior repair**		**Anterior and Posterior repair**	
	n=121		n=68		n=63	
How bothersome are the following symptoms for you?	Preop	1 year	Preop	1 year	Preop	1 year
Frequent urination		p<0.001		p= 0.03		p<0.001
Not at all	30 (25)	62 (51)	20 (29)	20 (29)	8 (13)	30 (48)
Slightly- mod	58 (48)	46 (38)	29 (43)	41 (60)	33 (52)	28 (44)
Greatly	27 (22)	0 (0)	16 (24)	0 (0)	19 (30)	0 (0)
Urine leakage related to urgency		p<0.001		p= 0.19		p= 0.002
Not at all	45 (37)	69 (57)	35 (51)	39 (57)	23 (37)	39 (62)
Slightly- mod	50 (41)	47 (39)	19 (28)	23 (34)	26 (41)	20 (32)
Greatly	19 (16)	0 (0)	5 (7)	0 (0)	8 (13)	0 (0)
Urine leakage related to physical activity		p= 0.18		p= 0.49		p= 0.87
Not at all	50 (41)	59 (49)	37 (54)	36 (53)	26 (41)	30 (48)
Slightly- mod	59 (49)	39 (32)	18 (26)	21 (31)	27 (43)	25 (40)
Greatly	6 (5)	9 (7)	3 (4)	3 (4)	4 (6)	1 (2)
Small amounts of urine leakage		p= 0.08		p= 0.98		p= 0.17
Not at all	77 (64)	78 (64)	44 (65)	46 (68)	38 (60)	44 (70)
Slightly- mod	33 (27)	28 (23)	16 (24)	16 (24)	15 (24)	15 (24)
Greatly	3 (2)	0 (0)	0 (0)	0 (0)	3 (5)	0 (0)
Difficulty emptying bladder		p<0.001		p= 0.02		p<0.001
Not at all	43 (36)	76 (63)	30 (44)	33 (49)	21 (33)	40 (63)
Slightly- mod	57 (47)	25 (21)	25 (37)	27 (40)	28 (44)	15 (24)
Greatly	17 (14)	6 (5)	7 (10)	2 (3)	8 (13)	1 (2)
Pain lower abdomen or genital area		p<0.001		p= 0.38		p= 0.02
Not at all	85 (70)	94 (78)	48 (71)	53 (78)	41 (65)	47 (75)
Slightly- mod	24 (20)	13 (11)	9 (13)	8 (12)	14 (22)	8 (13)
Greatly	6 (5)	0 (0)	3 (4)	1 (1)	4 (6)	2 (3)
Summated UDI-6 score		p<0.001		p=0.03		p<0.001
Mean (SD)	5.4 (±3.9)	2.9 (±2.7)	4.4 (±2.3)	3.3 (±2.7)	5.9 (±3.8)	3.0 (±2.6)

Figures are frequency (%).All statistical comparisons between preoperative values and 1-year follow-up using the Wilcoxon signed rank test. Mod (moderately)

7.2 PAPER II

7.2.1 Patient characteristics

At baseline, 105 women were sexually active and at the one year follow-up the corresponding figure was 84. See Figure 11. Sexually active women were similar to not sexually active women regarding baseline characteristics with the exception of age; sexually active women were younger (Table 12).

Figure 11. Flowchart of patients included in paper II.

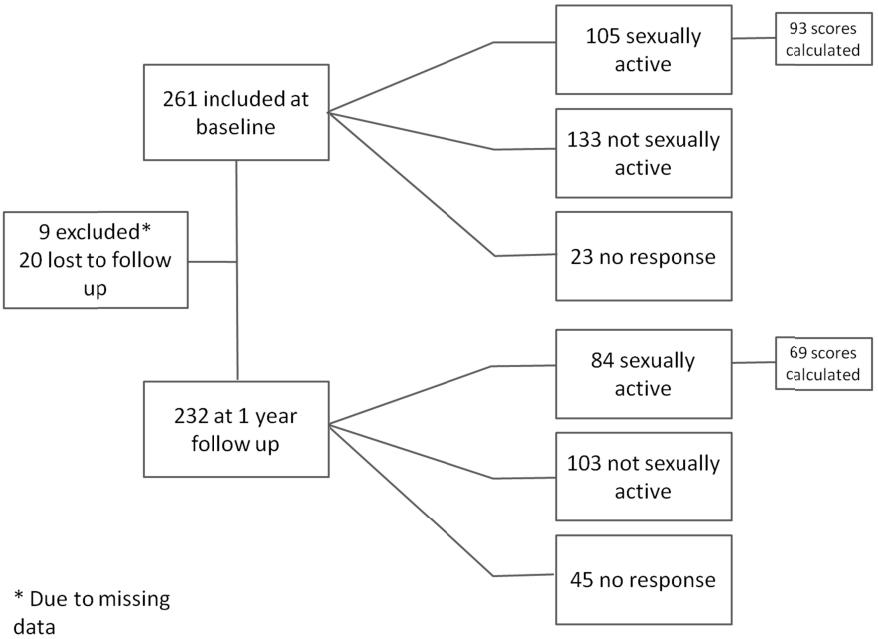


Table 12. Patient characteristics

N=261	Total no. of sexually active patients n=105	Total no. of non-sexually active patients* n= 133
Surgical procedure		
Anterior	46 (44)	66 (50)
Posterior	26 (25)	37 (28)
Anterior+posterior	33 (31)	29 (22)
Age	61.5 (±7.6 SD)	69.9 (±9.0 SD)
Parity	2 (range 1-6)	2 (range 0-7)
Body mass index	26.8 (±4.3 SD)	26.3 (±3.9 SD)
Smoker		
Yes	12 (11)	11 (8)
No	92 (88)	111 (83)
Menopausal		
Yes	94 (89)	110 (83)
No	7 (7)	3 (2)
Somatic diseases		
CVD	36 (34)	64 (48)
Thyroid dysfunction	9 (9)	21 (16)
Asthma and COPD	11 (11)	10 (8)
Arthrosis	6 (6)	7 (5)
Diabetes	3 (2.9)	8 (6)
Previous pelvic surgery		
Hysterectomy	58 (55)	64 (48)
Prolapse	43 (41)	69 (52)
Incontinence	8 (8)	12 (9)
Salpingo-oopherectomy	13 (12)	23 (17)
Other	10 (9)	7 (5)

SD, Standard deviation. COPD, chronic obstructed pulmonary disease

Numbers not adding up to 100% represent missing values.

Data are n (%) unless otherwise specified

* 23 patients did not respond to the question on sexual activity at baseline.

7.2.2 Subjective outcomes

There was an overall significant decrease in mean PISQ-12 scores when comparing pre- and postoperative average scores. A similar decrease was observed in all strata of independent variables: age at surgery, BMI, current cigarette smoking, menopausal status, childbirths, and concurrent surgery. Similarly, the decrease in PISQ-12 scores was noted regardless of anatomical postoperative stage and vaginal compartment (Table 13).

Table 13. PISQ-12 scores stratified by patient characteristics.

	Baseline **n= 93***	**1 year** **n= 69***	**p-value**
Overall	15.5 (±8.0)	11.7 (±6.9)	p< 0.001
Body mass index			
≤ 25	14.9 (±6.6)	12.5 (±6.2)	p= 0.04
>25	16.7 (±8.9)	11.9 (±7.2)	p= 0.006
Postmenopausal			
Yes	15.7 (±8.1)	12.0 (±7.1)	p< 0.001
No	17.4 (±8.8)	10.6 (±8.3)	p< 0.001
Smoker			
Yes	13.5 (±9.0)	12.5 (±7.8)	p= 0.2
No	16.2 (±7.9)	12.0 (±6.7)	p<0.001
Concurrent surgery			
Yes	15.3 (±7.4)	11.9 (±6.2)	p= 0.2
No	16.0 (±8.1)	12.2 (±6.8)	p< 0.001
Age			
≤ 65	16.0 (±8.4)	11.8 (±6.9)	p< 0.001
>65	15.6 (±7.0)	12.8 (±6.3)	p= 0.2
Parity			
1-2	15.6 (±8.4)	13.0 (±6.9)	p= 0.008
≥ 3	16.2 (±7.5)	10.8 (±6.0)	p= 0.01
Anterior transvaginal mesh repair			
POP-Q Stage 0-I	†	13.0 (±8.9)	NA
POP-Q Stage II-III	16.9 (±8.5)	12.8 (±8.7)	p= 0.01
Posterior transvaginal mesh repair			
POP-Q Stage 0-I	†	12.3 (±5.3)	NA
POP-Q Stage II-III	15.4 (±7.8)	12.5 (±5.5)	p= 0.08
Anterior transvaginal mesh repair	15.5 (±8.7)	12.3 (±8.0)	p= 0.03
Posterior transvaginal mesh repair	15.0 (±7.8)	13.5 (±5.3)	p= 0.2
Combined anterior and posterior transvaginal mesh repair	17.3 (±6.8)	10.7 (±5.5)	p= 0.002

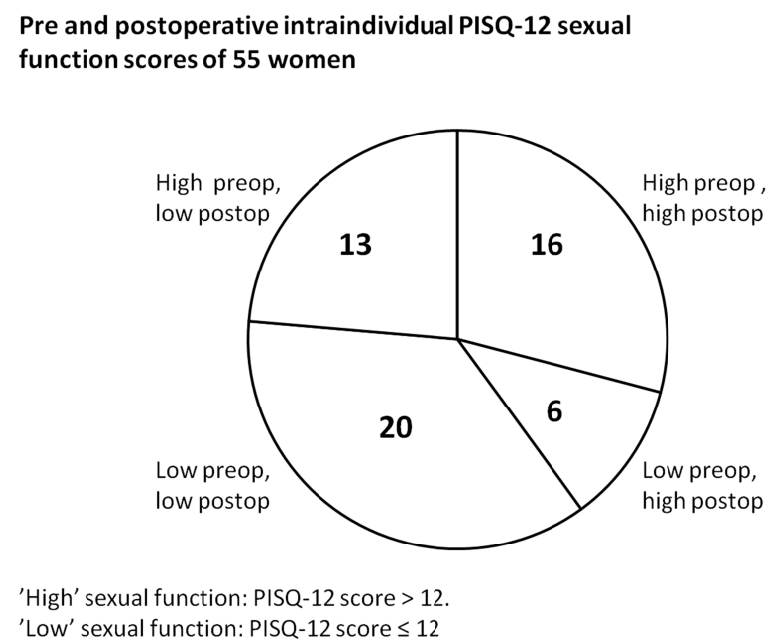
*Number of patients where a PISQ-12 score could be calculated. A summated score can be calculated with up to two missing values, after which the short form looses accuracy in predicting the full version.

†No patients available for analysis.

Statistical comparison between baseline and one year after surgery performed with Wilcoxon signed rank test.

An intra individual comparison between baseline and 1 year follow-up was possible for 55 women whose PISQ-12 questionnaires were available for both the pre- and post operative assessments. For the purpose of this study sexual function was defined as 'low' if the sexual score was ≤12 and 'high' if >12 (although the maximum score is 48 and' high' scores are otherwise generally well above the level of 12). Of these women, 29 had preoperatively a 'high' sexual function of which 13 moved to a 'low' sexual function postoperatively. However, 6 of the 26 women in the preoperative 'low' group moved to a 'high' sexual function postoperatively. Patient characteristics were similar between the 'high' and 'low' group.

Figure 12.PISQ-12 scores intraindividual comparison



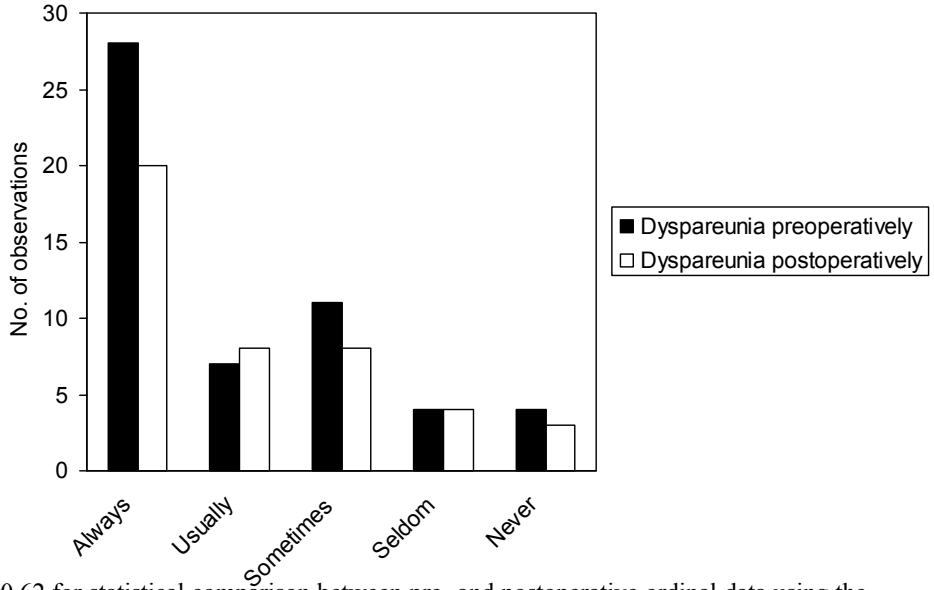
The forward multiple logistic regression analysis showed no significant predictors for low (12 or less) sexual function (Table 14).

Table 14. Relative risks (95% confidence intervals) for predictors of low (12 or less) sexual function scores

Predictors	**RR (95% CI)**
Age older than 65 years	1.5 (0.3–7.4)
Body mass index higher than 25	2.1 (0.5– 8.9)
Current cigarette smokers	8.9 (0.7–107.2)
Postmenopausal status	3.3 (0.1– 86.2)
More than two childbirths	0.7 (0.3–1.5)
Stage II or higher anterior prolapse postoperatively	1.1 (0.6 –2.0)
Stage II or higher posterior prolapse postoperatively	1.1 (0.7– 6.9)
Other concurrent surgery	1.9 (0.8 –7.3)
Vaginal exposure when characterized as present or absent	2.9 (0.8 –9.1)

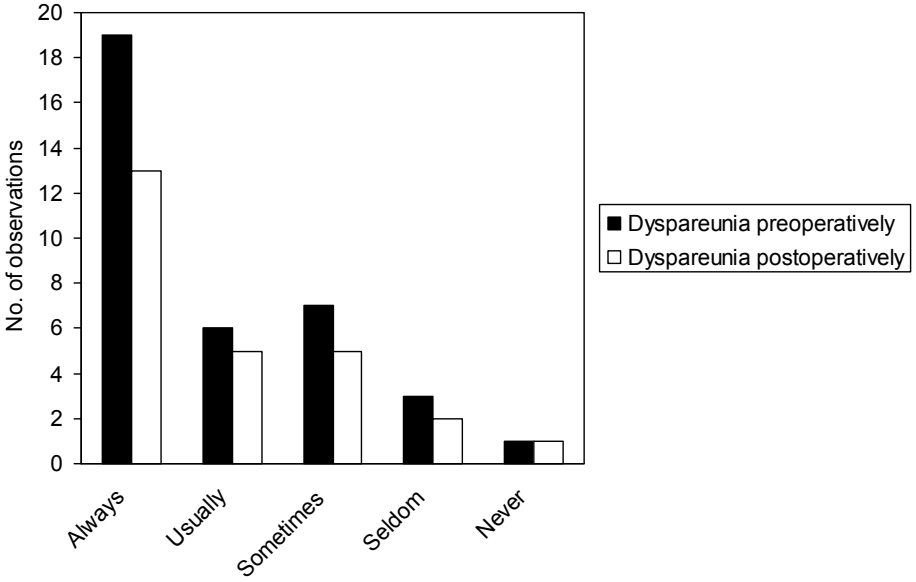
For the physical items, improvements were seen in ‘always fear of incontinence restricting sexual activity’ (82% compared with 63%, P<0.01) and ‘always avoidance of intercourse because of vaginal bulging’ (70% compared with 29%, p<0.001) whilst no significant changes were seen for ‘incontinence during sexual activity’ (62% compared with 56%, p=0.37) or ‘pain at intercourse’ (dyspareunia) (p=0.62 for anterior and P=0.13 for posterior mesh repair). Detailed results for dyspareunia are shown in Figures 13 and 14. Although generally non significant by themselves, there was an overall postoperative worsening of all behavioral– emotive and partner-related items.

Figure 13. Prevalence of dyspareunia after *anterior* transvaginal mesh repair



P=0.62 for statistical comparison between pre- and postoperative ordinal data using the Wilcoxon signed rank test.

Figure 14. Prevalence of dyspareunia after *posterior* transvaginal mesh repair



P=0.13 for statistical comparison between pre- and postoperative ordinal data using the Wilcoxon signed rank test.

7.3 PAPER III

7.3.1 Patient and control characteristics

10 patients and 8 controls were included in the study and the subject characteristics between the groups differed in several aspects: patients were older, had given birth to more children, were all postmenopausal, more often used hormone replacement therapy and had a higher BMI (Table 15). One baseline patient biopsy could not be assessed due to lack of epithelium. Patients were analyzed as their own controls in the pre- and postoperative evaluations.

Table 15. Descriptive group characteristics.

	Cases **n= 10**	**Controls** **n= 8**	**p-value**
Mean age (±SD)	67.1 (± 7.5)	42 (± 13.0)	p=0.002
Median parity (min,max)	2.5 (1-4)	1.3 (0-2)	p=0.06
Body mass index (±SD)	26.5 (± 4.8)	23.6 (± 4.0)	p=0.5
Menopause (%)	10 (100)	2	p<0.001
HRT (%)	4 (40)	0	p=0.07
Local estrogens (%)	3 (30)	0	p=0.1
Smoking (%)	0 (0)	0	p=1.0
Prolift			
Anterior (%)	4 (40)	-	NA
Posterior (%)	2 (20)	-	NA
Anterior+posterior (%)	4 (40)	-	NA

Comparison on non-parametric data using Mann-Whitney U-test and for proportions using χ^2.

7.3.2 Macroscopic inflammatory assessment.

There were no statistically significant changes in macroscopic inflammatory grading assessment postoperatively, although several cases of granuloma formation and exposure were observed (Table 18). Three cases of mild granuloma formation and 2 of mild exposure were detected but neither resulted in a surgical intervention. There were no cases of serious mesh related complications or mesh exposure/extrusion.

7.3.3 Microscopic assessment

Baseline histological counts and morphological grading in patients and controls were similar unless otherwise stated below.

Total cell content in the subepithelial tissue
(Table 16) At one year the total cell count decreased significantly compared with preoperative counts (p= 0.02). Controls had a higher total cell count than patients (p= 0.05).

Epithelial thickness
(Table 17) Epithelial thickness, DP height and width, and the distance between the DPs showed little variation at 1 year of follow up. Compared with the baseline assessment and to controls there were no significant differences in epithelial characteristics 1 year after surgery using polypropylene mesh

Manual cell counts
(Figure 15 and Table 16) There was a significant increase in macrophage and mast cell counts 1 year postoperatively (p= 0.03 and 0.01, respectively). Cells involved primarily in the humoral immune response, including monocytes, granulocytes, lymphocytes and plasma cells did not change significantly postoperatively although a decrease was seen in the number of fibroblasts (p= 0.04)

Semiquantitative grading of inflammation, vasculitis and collagen density
(Table 18) The average inflammatory cell infiltration increased although at a non significant level and no changes were seen in the assessment of vasculitis when comparing preoperative and postoperative grading (p= 0.2 and 1.0, respectively). There were no significant differences between preoperative and postoperative assessments of collagen density at the mesh-tissue interface (p= 0.2). With regard to baseline, inflammatory cell infiltration expression in controls was significantly higher than in patients.

Elastin area fraction
(Table 18) There were no significant differences between preoperative and postoperative assessments of elastin area fraction at the mesh-tissue interface (p= 0.3). Patients had a higher elastin area fraction count than healthy controls (p= 0.006)

Figure 15. Manual cell counts (N.B. the y-axis starts at 150)

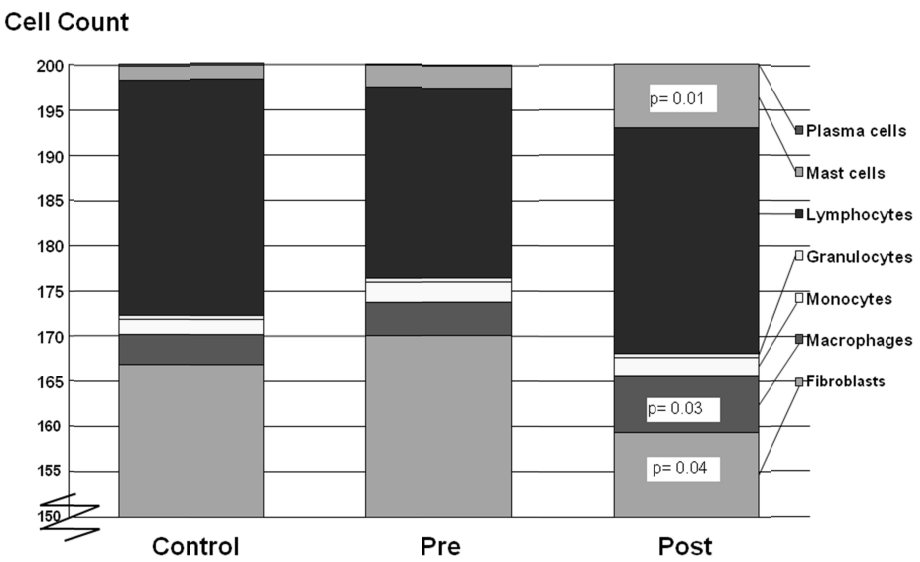


Table 16. Histological analyses and comparisons.

	Controls n=8		**Patients preoperatively n= 9**		**Patients Postoperatively n=10**		**Comparison between controls and patients preoperatively**	**Comparison between pre- and postoperative counts**
	Mean	±SD	Mean	±SD	Mean	±SD	p-value	p-value
Total cell count‡	0.0004	0.0001	0.0003	0.00005	0.0002	0.00006	p= 0.05	p= 0.02
Fibroblasts (%)	166.8 (83.4)	10.7	170 (85.0)	11.5	159.3 (79.7)	12.6	p= 0.5	p= 0.04
Macrophages (%)	3.4 (1.7)	3.0	3.78 (1.9)	2.6	6.2 (3.1)	4.2	p= 0.6	p= 0.03
Monocytes (%)	1.6 (0.8)	1.3	2.11 (1.1)	1.4	2.1 (1.1)	1.5	p= 0.5	p= 1.0
Granulocytes (%)	0.5 (0.25)	0.8	0.44 (0.2)	1.0	0.4 (0.2)	0.7	p= 0.6	p= 0.9
Lymfocytes (%)	26.0 (13)	8.8	21.22 (10.6)	9.1	25 (12.5)	9.64	p= 0.3	p= 0.4
Mast cells (%)	1.6 (0.8)	1.9	2.33 (1.2)	1.4	7 (3.5)	4.47	p= 0.3	p= 0.01
Plasmacells (%)	0.1 (0.07)	0.4	0.11 (0.1)	0.3	0 (0)	0	p= 0.9	p= 1.0
Celltypes (%)	200 (100)		200 (100)		200 (100)			

Statistical comparison between cases and controls using Mann-Whitney U-test and for comparison between pre- and postoperatively in patients using Wilcoxon signed-rank test. ‡Numerical density per μm^2.

Table 17. Epithelial measurements in patients and controls.

	Controls n=8	**Cases preoperatively n=9**	**Cases postoperatively n=10**	**Comparison between controls and cases preoperatively**	**Comparison between pre- and postoperative measurements**
				p-value	**p-value**
Distance from basement layer to surface	436.2±160.6	398.6±127.5	431.6±172.4	0.6	0.8
Distance from top of DP to surface	317.5±132.2	301.7±114.9	320±165.8	0.9	0.9
DP width	171.9±233.7	66.1±19.7	119.7±73.5	0.3	0.4
Distance between DP tops	293.4±140.4	316.7 ±357.1	693.7±571.7	0.2	0.4

Figures are mean (μm) ± SD. DP denotes dermal papillae.

Statistical comparison between patients and controls using Mann-Whitney U-test and for comparison between pre- and postoperatively in patients using Wilcoxon signed-rank test.

Table 18. Semi-quantitative, image analysis and macroscopic assessment.

	Controls n=8		**Patients preoperatively** n=9		**Patients postoperatively** n=10		**Comparison between controls and patients preoperatively**	**Comparison between pre- and postoperative counts**
Semi-quantitative and image analyses							p-value	p-value
Inflammatory cell infiltration†	1.5	(0-4)	0	(0-0)	0.5	(0-3)	p= 0.02	p= 0.2
Vasculitis†	0	(0-0)	0	(0-0)	0	(0-0)	p= 0.2	p= 1.0
Collagen density†	3	(1-3)	2.5	(2-3)	2	(0-3)	p= 0.4	p= 0.2
Elastin area fraction %‡	3.18	(3.67)	8.61	(2.64)	7.52	(3.75)	p= 0.006	p= 0.3
Macroscopic inflammatory grading								
Anterior compartment	No inflammatory reactions		No inflammatory reactions		3 mild granuloma and 1 mild exposure		NA	p= 0.2
Middle compartment	No inflammatory reactions		No inflammatory reactions		2 mild granuloma and 1 mild exposure		NA	p= 0.2
Posterior compartment	No inflammatory reactions		No inflammatory reactions		3 mild granuloma		NA	p= 0.5

Statistical comparison between cases and controls using Mann-Whitney U-test and for comparison between pre- and postoperatively in patients using Wilcoxon signed-rank test. Figures are: †Median (range); 0= none; 1=mild, 2=moderate; 3=pronounced; 4=severe. ‡Mean (SD)

7.4 PAPER IV

7.4.1 Patient characteristics

A total 353 patients having had anterior mesh kit repair for anterior pelvic organ prolapse were included in this secondary analysis. Data on inflammatory response was available for 337/353 patients (95%) at baseline, 351/353 (99%) at 2 months and 349/353 (99%) women at the 1 year follow-up. Mean age at surgery was 65.3 years (±9.6 SD), mean body mass index (BMI) was 26.5 kg/m^2 (± 3.8 SD) and median parity was 2 (range 0-7). The procedure was performed for prolapse recurrence in 129/353 patients (36.5%). There were 37 smokers (10.5%) and the number of women suffering from somatic inflammatory disease was 12 (3.4%) of which rheumatic disease was the predominant diagnosis (Table 19).

Table 19. Patient characteristics

	Anterior repair using the Prolift® system *n= 353*
Age (y)	65.3 ± 9.6
Parity	2 (0-7)
Body mass index	26.5 ± 3.8
Educational level*	
Compulsory school	195 (55.2)
High school	50 (14.2)
College/ university	87 (24.6)
Annual income (€)*	
Less than 10 000	52 (14.7)
10 000 - 30 000	213 (60.3)
30 000 - 40 000	15 (4.2)
More than 40 000	12 (3.4)
Smoker*	
Yes	37 (10.5)
No	311 (88.1)
Menopausal*	
Yes	292 (82.7)
No	60 (17.0)
Local or systemic hormone treatment*	
Yes	245 (69.4)
No	18 (5.1)
Somatic diseases	
Systemic inflammatory disease	12 (3.4)
Diabetes	8 (2.3)
Any previous prolapse surgery	129 (36.5)

Data are mean ± standard deviation, median (range) or n (%) *
Figures not adding up to 353 or 100% represent unavailable data

7.4.2 Mesh reactions

Inflammatory reactions at baseline were attributed to mechanical prolapse devices i.e. pessaries. Compared to baseline, the total number of patients with any type of inflammatory reaction to the mesh was 31.3% (110/351, p=0.000) at 2 months follow-up and thereafter decreased to 16.0% (56/349, p=0.001) at 1 year. Granulomas and exposures were the most commonly observed inflammatory reactions at 2 months. At the 1 year assessment compared with baseline, the number of granulomas (4.3%, p=0.010) showed a tendency to decrease compared with 2 months (18.8% p=0.001) whereas the number of exposures persisted (8.6%, p=0.003) (Table 20).

The number of cases with infections, necrosis and mesh extrusions were very few and there were no significant changes at 1 year compared to baseline or 2 months follow-up. Aside from one severe mesh reaction, most mesh related adverse events were in the range of mild-moderate severity and were managed conservatively. Surgical intervention because of mesh exposure during the one year follow-up was reported in a total of 11/353 patients (3.1%): five patients in the cohort study and 6 patients in the randomized controlled trial. No significant difference was observed when comparing mesh exposures at one year in patients undergoing primary or repeat surgery for anterior wall prolapse (7 vs. 23 exposures, p=0.15).

Table 20. Macroscopic assessment of clinical inflammatory reaction to anterior transvaginal mesh.

	Pre-operatively *n=337**		2 months *n=351**			1 year *n=349**		
	No. of patients (%)	**Median severity (range)**	**No. of patients (%)**	**Median severity (range)**	**P-value**	**No. of patients (%)**	**Median severity (range)**	**P-value**
Any kind of reaction	21 (6.2)		110 (31.3)		0.000	56 (16.0)		0.001
granuloma	4 (1.2)	0 (0-2)	66 (18.8)	0 (0-3)	0.000	15 (4.3)	0 (0-2)	0.010
exposure	12 (3.6)	0 (0-3)	25 (7.1)	0 (0-3)	0.018	30 (8.6)	0 (0-4)	0.003
necrosis	1 (0.3)	0 (0-1)	9 (2.6)	0 (0-2)	0.017	3 (0.9)	0 (0-2)	0.201
infection	3 (0.9)	0 (0-2)	7 (2.0)	0 (0-2)	0.028	1 (0.3)	0 (0-2)	0.584
extrusion	1	0 (0-1)	3 (0.9)	0 (0-2)	0.109	7 (2.0)	0 (0-2)	0.093

Statistical comparison with preoperative values for 2 months and 1-year follow-up using the Wilcoxon signed rank test. *Figures not adding up to 353 represent unavailable data

7.4.3 Risk factors for exposures

In the stratified analysis, the number of exposures seen at one year was greater for smokers than for non smokers (p= 0.02) and for patients suffering from somatic inflammatory disease compared to non sufferers (p= 0.03) (Table 21). Mesh exposures occurred among 7/37 smokers but showed no clear pattern with regard to those who smoked 0-5 cigarettes/day (2 exposures), 5-10 cigarettes/day (2 exposures), 10-20 cigarettes/day (2 exposures) or >20 cigarettes/day (1 exposure). There were no significant differences in the number of exposures in relation to age, parity, smoking, BMI, postmenopausal status, concurrent surgery or previous prolapse surgery.

Table 21. Mesh exposures at 1 year stratified by patient characteristics

	No. of patients at one year	Patients with exposures at one year	%	P-value
Overall	349	30	8.60	
Age				
≤ 65	182	15	8.24	0.66
>65	167	15	8.98	
Parity				
≤ 2	215	14	6.51	0.08
>2	134	16	11.94	
Body mass index				
≤ 25	152	12	7.89	0.75
>25	197	18	9.14	
Postmenopausal				
Yes	288	26	9.03	0.60
No	60	4	6.67	
Smoker				
Yes	37	7	18.92	0.02
No	307	23	7.49	
Concurrent surgery				
Yes	38	4	10.53	0.63
No	311	26	8.36	
Somatic inflammatory disease				
Yes	12	3	25.00	0.03
No	264	20	7.58	
Diabetes				
Yes	8	0	0.00	0.40
No	264	23	8.71	
Previous prolapse surgery				
Yes	126	7	5.56	0.98
No	65	4	6.15	

Figures not adding up to 349 or 100% represent unavailable data

Statistical comparison of exposures at 1 year grouped by patient characteristics using the Mann-Whitney U test

Uni- and multivariate logistic regression analysis for risk factors used age (>65 years), smoking (yes/no), postmenopausal status (yes/no), body mass index (>25kg/m2), parity (>2 children), and somatic inflammatory disease as independent univariate variables (Table 22). Following adjustment for age, parity, body mass index, and menopausal status, significant associations with mesh exposures remained at 1 year for smoking (OR 3.48, 95% CI 1.18-10.28) and somatic inflammatory disease (OR 5.11, 95% CI 1.17-22.23). The non-significant association between parity and exposures in the univariate analysis became significant when adjusting for the other independent

variables. No significant interaction was observed between smoking, parity and somatic inflammatory disease.

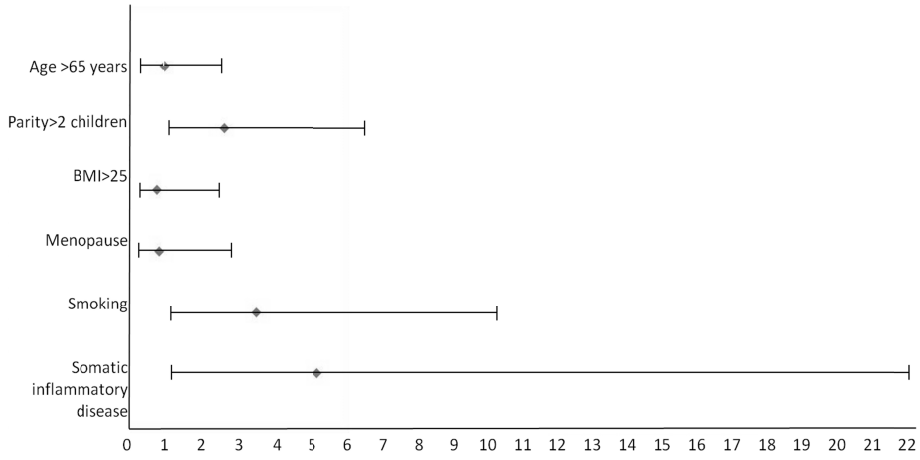
Table 22. Odds ratios of mesh exposures at one year for independent variables

	Univariate unadjusted OR	**95% CI**		**Adjusted OR***	**95% CI**	
		Lower	Upper		Lower	Upper
Age >65 years	1.18	0.56	2.51	1.04	0.42	2.59
Parity>2 children	1.93	0.91	4.12	2.64	1.07	6.51
BMI>25	1.13	0.53	2.44	0.83	0.34	2.05
Menopause	1.34	0.45	4.01	0.89	0.27	2.91
Smoking	2.90	1.14	7.37	3.48	1.18	10.28
Somatic inflammatory disease	4.12	1.01	16.79	5.11	1.17	22.23

*Multivariable model adjusted for independent variables unless the variable was the subgroup-defining variable.

BMI denotes body mass index in kg/m^2, OR odds ratio, CI confidence interval.

Figure 16. Predictors of mesh exposures at one year



OR and 95% confidence intervals on x-axis

8 DISCUSSION

8.1 SUBJECTIVE AND OBJECTIVE CLINICAL OUTCOMES

Trocar guided transvaginal mesh surgery for pelvic organ prolapse is associated with satisfactory subjective and objective clinical outcomes at 1 year. Anatomic cure rates ranged between 79-86% and the combined anterior and posterior procedure was associated with the most effective restoration of vaginal support. This could be a result of the added support provided to the upper vagina by the posterior procedure. Since more than half of all elderly women show signs of stage II prolapse,(1) the definition of anatomic success as stage 0-I used in this study can be debated. Had we used a more lenient definition, success rates would of course have been even higher. The superior overall anatomic cure rates of 95% observed in a study by Fatton et al may be explained by differences in study design, follow up time, and prolapse classification system.(11)

Compared with traditional pelvic organ prolapse repair, our study resulted in improved anatomic cure rates for anterior repair,(59, 95, 96) but similar cure rates for posterior repair,(97-99) This suggests that use of mesh provides a greater advantage in anterior repair whereas addition of mesh is less advantageous with regard to restoration of posterior vaginal topography. Improvements in subjective outcomes for all operated vaginal compartments were observed and sustained at the one year follow-up. Although patient satisfaction does not necessarily correlate to anatomic cure,(100, 101) we found an association between anatomic improvement and ameliorated symptoms.

The postoperative improvements in lower urinary tract dysfunction observed in this study were statistically significant, yet the clinical significance can be debated since the magnitude of the improvements were less than half of the standard deviations of the baseline values. The lack of improvement observed for stress urinary incontinence may theoretically be due to an overcorrection of the anterior vaginal wall and bladder neck caused by the mesh technique as discussed previously and corroborates findings in previous studies.

The number of adverse events observed in this study is comparable to other studies.(9, 80) The number of exposures persisted at one year, which is also comparable to other studies,(72, 102) although the number of surgical interventions needed for treatment of mesh exposures were fewer. A possible explanation for this was the routine use of preoperative topical estrogen in all patients before surgery and after the two month follow-up included in the study protocol. Furthermore the low rate of serious mesh complications can be attributed to the strict aseptic handling of the mesh, change of gloves in mid-surgery, use of intra operative antibiotic prophylaxis and the supervised hands-on training for all participating surgeons before study start.

The satisfactory subjective and objective outcomes observed in this prospective multicenter cohort study with a near 90% follow up rate, are comparable to results observed in randomized trials.(78, 103)

8.2 SEXUAL DYSFUNCTION

Sexual dysfunction scores deteriorated one year after trocar guided transvaginal mesh kit repair of pelvic organ prolapse. The deterioration was primarily observed for scores

in behavioral-emotive and partner-related items though not for dyspareunia in specific which was somewhat surprising. Although de Tayrac et al. showed a 13% increased rate of de novo dyspareunia following mesh repair, several studies (ours included) have not shown significantly increased rates of dyspareunia.(104) The divergent results on dyspareunia could be explained by differences in surgical techniques, differences in mesh texture or composition and use of different instruments to measure the rate of dyspareunia.

A negative trend in sexual scores was noted regardless of categorization of patient characteristics. Baseline scores were, however, fairly low to begin with and a 15% deterioration in sexual function scores is clinically difficult to interpret. In comparison to a study by Sentilhes et al.,(104) the women in our study had considerably lower baseline sexual function scores. Because there is a dirth of normative PISQ sexual function scores in various age categories of women we cannot say if our study population had a poorer sexual function as compared to the general population. If this is the case, some degree of selection bias was probably involved and surgeons may have been less inclined to include women with normal sexual function into the study. Even so not all women deteriorated in sexual function and some actually moved from poor sexual function in a positive direction after surgery. This corroborates studies which suggest that restoration of vaginal topography may actually improve sexual function in some patients.(105)

No specific predictors of poor sexual function related to surgery were found and although a post hoc power analysis indicated an adequate sample size for overall scores, specific independent variables may not have been adequately powered. The inclusion and exclusion criteria in our study add to the internal validity but one should bear in mind that considering our population characteristics our findings may not be generalised to pre menopausal or nulliparous women.

Sexual function scores in the present study were similar regardless of anatomic outcomes, and objective anatomical cure showed no correlation with sexual function. This has also been shown for traditional repair without mesh,(106) although others have found a positive association between anatomical success and sexual function after prolapse correction with mesh.(104, 105, 107) No concurrent continence procedures were performed at the time of prolapse repair in this study so any improvements in sexual function could not be explained by surgically improved continence.

It is known that a positive body image and self esteem are associated with better sexual function,(108) and although some studies have shown positive sexual results in general after vaginal surgery,(109, 110) studies focusing on emotional and partner related aspects are scarce. Future studies should focus not only on physical aspects of sexual dysfunction after prolapse surgery but also behavioral, emotional and partner related issues.

The risk of deteriorated sexual function seen in this study is corroborated by a recent randomized study by Altman reporting a greater risk of dyspareunia in the mesh group compared to the traditional repair group (7.3% vs 2%). However, another recent randomized study by Withagen saw no significant difference in dyspareunia between the groups (8% vs 10%).(78, 103)

8.3 HISTOLOGICAL INFLAMMATORY RESPONSE

A certain degree of inflammatory response is to be expected when placing a foreign body into the human body, but this is to our knowledge the first human in vivo study assessing inflammatory reactions to large sized mesh for pelvic organ prolapse. Although previous studies have been performed in rodents,(111) it is questionable whether data can be extrapolated to humans considering the unique human vaginal environment and dynamics. Human histological studies on the other hand are ethically limited by the number of participants. This study was novel and pilot like in nature similar to a previous study on mesh used for sling procedures,(6) and therefore no power analysis was performed and patients and controls were not matched according to age, parity or menopause.

We found a postoperative increase in macrophages and mast cells at one year after surgery suggesting an activation of a persistent cellular foreign body response. Phagocytosis of foreign body material or microbes is the primary role of macrophages together with antigen presentation and secretion of cytokines. Mast cells are major effector cells of hypersensitivity reactions, reside adjacent to blood vessels and degranulate inflammatory mediators such as histamine. The increase in semiquantitative grading of inflammatory cell infiltration, although non-significant, also suggests a mild inflammatory response to the mesh. This is also in agreement with rat studies suggesting that type I mesh causes a mild inflammatory reaction.(112) Cells actived primarily in infectious responses, such as lymphocytes, were unaltered postoperatively indicating that the histologic reaction was of a non infectious type. The largely unchanged epithelial measurements also corroborates the finding of an inflammatory response of low intensity and corresponds to the few cases of severe clinical mesh reactions in the larger study.(113)

A slight decrease in total cell count and number of fibroblasts was observed one year postoperatively suggesting that healing and scar formation was completed. No adverse influence on connective tissue metabolism was found as reflected by the statistically unchanged elastin area fraction and collagen density postoperatively. Mesh- host issue integration could not be assessed as no direct mesh biopsies were taken from the mesh in order to avoid risks of infection or exposure.

Elastin area fraction counts were higher in women with pelvic organ prolapse compared to controls, suggesting an etiologic role for elastin in the development of pelvic organ prolapse. Total cell counts and inflammatory cell infiltration also differed between the two groups and an explanation could be the differences in population characteristics such as age and menopause. However, cell counts in specific were similar in patients and controls so it is plausible that the observed increase in macrophages and mast cells was attributed to mesh reactions. This is in concurrence with other reports,(112, 114) and is strengthened by the use of blinded histopathologist.

The macroscopic clinical inflammatory grade was in agreement with the microscopic findings suggesting a satisfactory biocompatibility of large transvaginal mesh used for pelvic organ prolapse. That said, a persistent mild foreign body reaction was observed and the long-term effects remain unknown.

8.4 PREDICTORS OF MESH EXPOSURES

The prevalence of mesh exposures (and granuloma) increased one year after surgery and increased significantly in women with more than 2 children, cigarette smokers and

somatic inflammatory disease. In comparison to clinical studies, register based assessments of the prevalence of exposures and other complications pertaining to prosthetic surgical prolapse repair have so far been limited by the lack of information on the total number of performed procedures. Strengths of the present study include the prospective study design, the uniform surgical protocol, the low number of concomitant procedures and a homogenous outcome measure. The overall exposure rate was consistent with those reported by other investigators.(115) The relatively high exposure rates seen in the study by Nieminen et al. may partly be explained by the placement of mesh between the endopelvic fascia and mucosa instead of beneath the fascia.(116)

The association between exposures and multiparity may be an effect of vaginal tissues losing resilience after childbirth and as a result are susceptible to mesh exposure. However, the finding should be interpreted with caution since multiparity was not a risk factor in the stratified or univariate analysis which may indicate a chance finding due to insufficient sample size or large within group variation.

The proportion of smokers in our population was comparable to Swedish population statistics for women over 64 years.(117) It is known that smoking is associated with increased post operative morbidity,(118) and in a recent Swedish trial, smoking cessation preoperatively decreased the risk of acquiring post operative complications.(119) Cundiff and Lowman found smoking to be a risk factor for mesh exposure in patients undergoing abdominal sacral colpopexy.(120, 121) Studies on the effects of smoking in transvaginal mesh surgery are few,(72) but largely concur with the results of the present study.

Postoperative wound healing,(122, 123) connective tissue metabolism, collagen synthesis and epithelial regeneration,(124) have all been shown to be affected by smoking, as well as tissue oxygenation, peripheral vasoconstriction, immune cell response,(125, 126) and the progesterone estrogen ratio,(127) All of these factors may influence mesh biocompatibility and thus be adversely affected by tobacco smoking. Previous studies suggest that the risk of mesh exposures is influenced by age, BMI,(72, 128) concomitant hysterectomy and surgical incision in proximity to the mesh.(73)

Vaginal epithelial maturity may influence reactions to implants. The use of pre- and postoperative local estrogens in both studies aimed to improve the condition of the vaginal epithelium but no specific measurements of epithelial maturity were performed. Studies using karyopycnotic indexing or vaginal pH may provide additional information on epithelial reactions to synthetic mesh.

Although somatic inflammatory diseases such as rheumatoid arthritis, Sjögren's disease and lupus erythematosus have more or less different pathoetiologies, they also have similar characteristics such as multiple organ involvement, afflicted connective tissues and underlying autoimmune mechanisms. These traits accompanied by immunosuppressant medications may prolong wound healing and influence human host-vs-implant reactions. The number of patients with somatic inflammatory disease in our study was small (indicated by wide confidence intervals) and the association is in need of corroboration in further studies.

It remains to be determined if the rather simple intervention of pre- and perioperative smoking cessation, may contribute to a decrease in the rate of mesh complications when used for pelvic reconstructive surgery. In any case, smoking cessation should be integrated as one component in a broader prevention strategy to reduce mesh complications.

9 CONCLUSIONS

The specific aims and conclusions were:

1. *Aim*: To prospectively investigate the clinical outcomes one year after pelvic organ prolapse repair using a trocar-guided mesh kit. *(Paper I)*

   Conclusion: Standardized trocar-guided transvaginal mesh techniques can be performed in a multicenter setting with a relatively low rate of serious surgical complications and with satisfactory subjective and objective outcomes.

2. *Aim*: To prospectively study the sexual outcomes one year after pelvic organ prolapse repair using a trocar-guided mesh kit. *(Paper II)*

   Conclusion: There is a risk for sexual dysfunction based on emotional-behavioral and partner- related issues after transvaginal mesh kit repair of pelvic organ prolapse.

3. *Aim*: To investigate the histological inflammatory response one year after transvaginal pelvic organ prolapse repair using mesh. *(Paper III)*

   Conclusion: There is a mild but persistent histological foreign body reaction after pelvic organ prolapse surgery with large macroporous monofilament polypropylene mesh.

4. *Aim*: To assess potential risk factors associated with the development of exposures one year after transvaginal pelvic organ prolapse repair using mesh. *(Paper IV)*

   Conclusion: Smoking, multiparity and somatic inflammatory diseases are possible risk factors for mesh exposures after trocar guided anterior mesh kit repair for pelvic organ prolapse.

10 POPULÄRVETENSKAPLIG SAMMANFATTNING

Framfall är en benign sjukdom som medför att slidans väggar och organen innanför buktar in i och ibland ut ur slidan. Hos dessa kvinnor har vaginas stödjestrukturer förlorat sin hållbarhet och spänst. Symptomen inkluderar tyngd- tryck- eller utfyllnadskänsla i vagina men kan även innefatta symptom från bäckenorganen som blåstömningssvårigheter, överaktiv blåsa, sexuell dysfunktion samt tarmtömningssvårigheter. Symptomen leder ofta till en betydande försämring av den drabbade kvinnans livskvalitet. Omkring 50% av alla kvinnor som har fött barn har någon form av framfall, och livstidsrisken att genomgå operation pga framfall eller urininkontinens har estimerats till ca 11%.

Det är inte helt klarlagt vad som orsakar framfall men kopplingar finns till graviditet, barnafödande, tillstånd med ökat buktryck (t.ex. fetma, kronisk obstruktiv lungsjukdom, tungt arbete) samt ärftliga faktorer. Standardbehandlingsmetoden är en kirurgisk teknik där man försöker återskapa stödet för vagina. Metoden har funnits i över 100 år men har visat sig ge otillfredsställande långtidsresultat och på grund av recidiv tvingas upp emot 30-50% av alla kvinnor som genomgår traditionell framfallskirurgi att genomgå ytterligare ingrepp.

Vid ljumskbråckskirurgi och urininkontinenskirurgi har kraftigt förbättrade operationsresultat uppnåtts vid användning av syntetiskt polypropylennät som stöd för den sviktande vävnaden. Till följd av detta föreligger en utbredd användning av syntetiskt implantat även vid framfallsoperationer trots att man ännu inte bevisat eventuella fördelar för användning i detta område. Betingelserna i slidan är annorlunda, slidan har en annan miljö och funktion än ljumsken, och nätet är mycket större än det som används vid inkontinenskirurgi. Därför kan man inte förbehållslöst anta att implantat är lika framgångsrika vid framfallskirurgi som vid ljumskbråcks- eller inkontinenskirurgi. Det är hittills ont om studier som har studerat resultaten av framfallskirurgi med syntetiska nät vid framfall och studierna i denna avhandling ämnar belysa både kliniska och histologiska utfall vid framfallsoperation med syntetiskt nät.

I den första studien i denna avhandling har flera kliniker i de nordiska länderna samarbetat i en prospektiv kohortstudie. 261 kvinnor med framfall inkluderades och genomgick operation med ett syntetiskt nät där nätet placerades med hjälp av metalledare för att åtgärda framfallet i framvägg, bakvägg eller både och. De undersöktes gynekologiskt och fick fylla i enkäter angående prolaps och inkontinenssymptom samt livskvalitet före operation, efter 2 månader och 1 år. Vi fann att det anatomiska resultatet var bra efter 1 år, att kvinnorna var nöjda med operationsresultatet, och att livskvaliteten hade förbättrats dock inte beträffande symptom som rörde ansträngningsurininkontinens. I samband med operation noterades en relativt låg frekvens av allvarliga komplikationer men vid ett år konstaterades att nätet hade blivit exponerat i slidan hos drygt en tiondel av patienterna.

Den andra studien använde sig av samma patientgrupp som ovan men kvinnorna fick i stället besvara en enkät beträffande sexuella vanor före operation och efter 1 år. Vi fann att bara 105 av kvinnorna var sexuellt aktiva från början och efter operation var 84 sexuellt aktiva. Dessa kvinnor var något yngre än de som inte var sexuellt aktiva men i övrigt fanns det inga skillnader mellan grupperna. Efter operation såg vi en försämring i sexuell funktion oavsett vikt, ålder, antalet barn, framfallsnivå, vilken del

av slidan som opererades eller operationsresultat. Enstaka kvinnor förbättrades i sexuell funktion men generellt skedde en försämring där den största försämringen sågs i frågor rörande beteende, känslor samt partnerrelaterade frågor. Ingen försämring sågs för frågor rörande smärta vid sexuell aktivitet (dyspareuni).

I den tredje studien undersöktes slidans cellulära reaktion på framfallsnät. Från Danderyds Sjukhus i Stockholm inkluderades 10 kvinnor som hade framfall och som skulle genomgå operation med nät samt 8 kvinnor utan framfall som var planerade för annan kirurgi i bäckenet. Alla genomgick gynekologisk undersökning och vävnadsprovtagning från slidväggen i samband med operation. De 10 kvinnorna som framfallsopererades genomgick även gynekologisk undersökning och vävnadsprovtagning från slidväggen i lokalbedövning efter 1 år. Vävnadsproverna analyserades histologiskt och vi fann att jämfört med före operation förelåg en ökad låggradig inflammation vid 1 år. Mängden stödjevävnad och epiteltjocklek hade inte förändrats, dock förelåg en skillnad jämfört med de friska kontrollerna vilket tyder på att det möjligen finns en koppling mellan framfall och stödjevävnad. De histologiska fynden stämde överens med de tecken på inflammation och nätexponering som sågs vid den gynekologiska undersökningen.

Den fjärde studien fokuserade på exponering eller utträngning av nätet och vilka faktorer som kan tänkas påverka denna risk. De patienter från första studien som hade genomgått operation på främre slidväggen samt samtliga patienter från en senare randomiserad studie som också hade opererats med nät i främre slidväggen inkluderades, totalt 349 patienter. Nätexponering sågs hos 8,6% av patienterna och vidare analys identifierade rökning, reumatisk sjukdom och fler än två barn som riskfaktorer för exponering.

De fyra studierna i denna avhandling har funnit att standardiserade framfallsoperationer med nät kan genomföras med relativt få allvarliga kirurgiska komplikationer och med tillfredsställande subjektiva och objektiva resultat. Det föreligger dock en risk för att den sexuella funktionen försämras framförallt beträffande frågor rörande beteende, känslor samt partnerrelaterade frågor. Nätreaktioner kan förklaras av en inflammatorisk cellulär reaktion snarare än infektionrelaterade cellulära reaktioner. Vi har också sett att rökning, rheumatiska sjukdomar och fler än två barn ökar risken för nätkomplikationer. Beslutet om operation för framfall är komplext och måste väga in all tillgänglig information om kvinnans symptom, framfallets natur och de olika framfallsingreppens för- och nackdelar i både det korta och långa loppet. Vid användning av nät vid framfallsoperation bör därför potentiella risker och vinster noggrant övervägas.

11 ACKNOWLEDGEMENTS

This thesis has come about thanks to the unending support and friendship from many people both near and far. In particular I would like to thank the following;

The *patients* and *controls* who took part in the studies.

The *Nordic Transvaginal Mesh Group* doctors who performed all surgeries.

Associate Professor *Daniel Altman*, principal tutor, supervisor and friend, whose relentless energy, experience and perseverance have impressed and encouraged me to perform way beyond my personal perceived ability. I am equally impressed and inspired by his amazing wife *Maria Altman* and family.

Associate Professor *Christian Falconer*, tutor and co-author, not only for his expertise, skills and connections in the field of urogynecology but also for his wisdom and insights, for being down to earth and empathetic.

Doctor *Bo Blomgren*, tutor and co-author, pathologist at Research and Development Astra Zeneca, for his unmatched expertise in the field of unbiased stereology, vaginal pathology and not to mention amateur radio and kusmi tea.

Doctor *Anders Hallin*, tutor and co-author, urologist at Löwenströmska and Danderyd Hospital for his invaluable eye for detail, his logic reasoning and inspiring ambition to apply evidence in all he undertakes.

Associate Professor *Johanna Albert*, Head of the Department of Surgery and Urology and Doctor *Staffan Gröndal*, former Head of the Department of Surgery and Urology at Danderyd Hospital for supporting my clinical endeavors and for providing a positive environment for research.

Doctor *Elisabeth Nelson*, Head of the Division of Urology at Danderyd Hospital, whose enviable clinical and logistical skills have provided me with inspiration and time, not only for clinics and research but also for my family.

Professor *Erik Näslund*, Head of the Department of Clinical Sciences, Karolinska Institute at Danderyd Hospital, for creating and maintaining exceptional scientific conditions at Danderyd Hospital.

Associate Professor *Håkan Wallén*, Deputy Head of the Department of Clinical Sciences, Karolinska Institute at Danderyd Hospital, for his dedication to providing and demanding a high scientific and educational standard in the PhD education.

My co-authors *Anju Zhang, Marie Ellström Engh, Susanne Axelsen, Tapio Väyrynen, Pentti Kiilholma, Ingebjørg Kinne, Gunilla Tegerstedt*, and *Gregor Larsson* for

valuable contributions to my manuscripts, as well as, emergency requisitions of important documents.

Charlotte Wistrand, Gunilla Zetterström, and the research team of the Division of Obstetrics and Gynecology at Danderyd Hospital for uncontested organizational skills and cheerful support.

Marion Ek, friend, colleague and ally, for sharing, for your urogynecological tricks and skills and for being warm, incredibly enthusiastic and encouraging.

All amazing *colleagues* and *friends* at the Department of Surgery and Urology and the Department of Obstetrics and Gynecology (especially those at the Division of Urology as well as the Pelvic floor team) for friendship and encouragement, and for keeping the hospital running 24-7.

My mentor *Niclas Hellman* not only for fantastic dinners and advice on taxes and grants but for sincere encouragement in research and life.

Dear friends and colleagues *Helena Kopp Kallner, Anna Drake, Helena Sackey, Anna Carin Horne, Lena Lindgren,* and previous roommate *Linda Waage* for love, caring, sharing, and understanding, (and for insisting that "research is a way to create time for family"….yeah right!)

My parents, *Gustav* and *Barbara* and my brothers *Christer* and *Peter* for always 'telling me what to do' (and I mostly did!), and for teaching me to always reach further. To my extended family *Anders* and *Solveig* for everyday support and friendship.

Finally, *Ingvar*, my incredible husband who so amazingly supports and encourages me yet also contests and challenges me. You have forced me to learn, grow and progress, not only as a researcher but also as a person.
Thank you also to our fantastic children; our family means everything to me.

The studies in this thesis were supported by grants from the *Johanna Hagstrand and Sigfrid Linné foundation* and the *Regional agreement on medical training and clinical research between Stockholm County Council and Karolinska Institute*.

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13 APPENDIX

13.1 QUESTIONNAIRES PAPER I

Urogenital Distress Inventory - Short form (UDI-6)

Do you experience, and, if so, how much are you bothered by	(0) not at all	(1) slightly	(2) moderately	(3) greatly
1) Frequent Urination?				
2) Urine leakage related to the feeling of urgency?				
3) Urine leakage related to physical activity, coughing or sneezing?				
4) Small amounts of urine leakage (drops)?				
5) Difficulty emptying your bladder?				
6) Pain or discomfort in the lower abdominal or genital area?				

Incontinence Impact Questionnaire - Short form (IIQ-7)

Has urine leakage and/or prolapse affected your	(0)not at all	(1) slightly	(2) moderately	(3) greatly
1) Ability to do household chores (cooking, housecleaning, laundry)?				
2) Physical recreation such as walking, swimming, or other exercise?				
3) Entertainment activities (movies, concerts, etc.)?				
4) Ability to travel by car or bus more than 30 minutes from home?				
5) Participation in social activities outside your home?				
6) Emotional health (nervousness, depression etc.)?				
7) Feeling frustrated?				

13.2 QUESTIONNAIRE PAPER II

Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-12)

Following are a list of questions about you and your partner's sex life. All information is strictly confidential. Your confidential answers will be used only to help doctors understand what is important to patients about their sex lives. Please check the box that best answers the question for you. While answering the questions, consider your sexuality over the past six months. Thank you for your help.

1. How frequently do you feel sexual desire? This feeling may include wanting to have sex, planning to have sex, feeling frustrated due to lack of sex, etc.

☐ Always (0) ☐ Usually (1) ☐ Sometimes (2) ☐ Seldom (3) ☐ Never (4)

2. Do you climax (have an orgasm) when having sexual intercourse with your partner?

☐ Always (0) ☐ Usually (1) ☐ Sometimes (2) ☐ Seldom (3) ☐ Never (4)

3. Do you feel sexually excited (turned on) when having sexual activity with your partner?

☐ Always (0) ☐ Usually (1) ☐ Sometimes (2) ☐ Seldom (3) ☐ Never (4)

4. How satisfied are you with the variety of sexual activities in your current sex life?

☐ Always (0) ☐ Usually (1) ☐ Sometimes (2) ☐ Seldom (3) ☐ Never (4)

5. Do you feel pain during sexual intercourse?

☐ Always (0) ☐ Usually (1) ☐ Sometimes (2) ☐ Seldom (3) ☐ Never (4)

6. Are you incontinent of urine (leak urine) with sexual activity?

☐ Always (0) ☐ Usually (1) ☐ Sometimes (2) ☐ Seldom (3) ☐ Never (4)

7. Does fear of incontinence (either stool or urine) restrict your sexual activity?

☐ Always (0) ☐ Usually (1) ☐ Sometimes (2) ☐ Seldom (3) ☐ Never (4)

8. Do you avoid sexual intercourse because of bulging in the vagina (either the bladder, rectum or vagina falling out)?

☐ Always (0) ☐ Usually (1) ☐ Sometimes (2) ☐ Seldom (3) ☐ Never (4)

9. When you have sex with your partner, do you have negative emotional reactions such as fear, disgust, shame or

☐ Always (0) ☐ Usually (1) ☐ Sometimes (2) ☐ Seldom (3) ☐ Never (4)

10. Does your partner have a problem with erections that affects your sexual activity?

☐ Always (0) ☐ Usually (1) ☐ Sometimes (2) ☐ Seldom (3) ☐ Never (4)

11. Does your partner have a problem with premature ejaculation that affects your sexual activity?

☐ Always (0) ☐ Usually (1) ☐ Sometimes (2) ☐ Seldom (3) ☐ Never (4)

12. Compared to orgasms you have had in the past, how intense are the orgasms you have had in the past six months?

☐ Much less intense (4) ☐ Less intense (3) ☐ Same intensity (2)
☐ More intense (1) ☐ Much more intense (0)

13.3 PARTICIPATING CENTERS

The Nordic Transvaginal Mesh group includes the follow study centers:

TVM 2

Sweden

Danderyd Hospital, Stockholm
Kristiansstad Hospital, Kristiansstad
S: t Göran Hospital, Stockholm
Linköping University Hospital, Linköping
Sahlgrenska University Hospital, Göteborg
Örebro University Hospital, Örebro
Västerås Hospital, Västerås
Skaraborg Hospital Skövde, Skövde
Ystad Hospital, Ystad
Uppsala University Hospital, Uppsala
Vrinnevi Hospital, Norrköping
South Hospital, Stockholm
Halmstad Hospital, Halmstad'

Finland

Turku University Hospital, Turku
Päisät-Hämes Central Hospital, Lahti
Jorvi Hospital, Espoo
Helsinski University Central Hospital
Lohja Hospital, Lohja.

Denmark

Skejby Hospital, Skejby
Nyköbing Hospital, Nyköbing

Norway

Akershus University Hospital, Ahus
Gjøvik Hospital, Gjøvik
Kongsberg Hospital, Kongsberg
Rikshospitalet, Oslo
Haukeland Hospital, Bergen
Asker & Bærum Hospital, Bærum
Regional Hospital in Tromsø, Tromsø.

TVM 3

Sweden

Danderyd University Hospital, Stockholm
Uppsala Academic Hospital, Uppsala
Sahlgrenska University Hospital, Gothenburg
South Hospital, Stockholm
S:t Göran Hospital, Stockholm
Hudiksvall Hospital, Hudiksvall
Karlstad Hospital, Karlstad
Sunderby Hospital, Luleå
Karlskoga Hospital, Karlskoga
Södertälje Hospital, Södertälje
Örebro University Hospital, Örebro

Västerås Hospital, Västerås
Ystad Hospital, Ystad
Skaraborg Hospital Skövde, Skövde
Vrinnevi Hospital, Norrköping
Sundsvall Hospital, Sundsvall
Linköping University Hospital, Linköping
Kristiansstad Hospital, Kristiansstad
Capio Läkargruppen Örebro, Örebro
Halmstad Hospital, Halmstad
Värnamo Hospital, Värnamo
Västervik Hospital, Västervik
NÄL Hospital, Trollhättan
Borås Hospital, Borås
Karolinska University Hospital Huddinge, Stockholm
Karslkrona Hospital, Karlskrona
Höglandssjukhuset, Eksjö

Finland

Hyvinkää Hospital, Hyvinkää
Jorvi Hospital, Espoo
Lohja Hospital, Lohja
Porvoo Hospital, Porvoo
Åbo Hospital, Åbo
Lapland Central Hospital, Rovaniemi
Central Finland Central Hospital, Jyväskylä
Kotka Hospital, Kotka
South Carelian Central Hospital, Lappeenranta

Denmark

Skejby Hospital, Skejby

Norway

Kongsberg Hospital, Kongsberg
Rikshospitalet, Oslo
Haukeland Hospital, Bergen
Bærum Hospital, Bærum
The Regional Hospital in Tromsø, Tromsø
Akershus University Hospital, Ahus
Telemark Hospital, Skien
Stavanger University Hospital, Stavanger
Namsos Hospital, Namsos
S:t Olav Hospital, Trondheim
Levanger Hospital, Levanger
Innlandet Hospital, Brumunddal
Ringerike Hospital, Hønefoss
Førde Hospital, Førde
Sørlandet Hospital, Flekkejord