The use of implants in female pelvic floor reconstructive surgery. Short and long term efficacy and safety.

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The use of implants in female pelvic floor reconstructive surgery

Short and long term efficacy and safety

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About the author

Originally from Thessaloniki, Greece, I left after my studies to explore my ambitions in Sweden. From Gothenburg, Sollefteå, Umeå and Sundsvall to Norrköping and Stockholm, my interest in operative gynecology grew and I found a channel to express it through urogynecology at the Skåne University Hospital. At the same time, the Faculty of Medicine at Lund University allowed me to delve deeper into this field with my PhD studies and research projects advancing hand in hand with my clinical work. Pelvic floor reconstructive surgery is a fascinating field that employs the principles of plastic surgery in a function-oriented and symptom-based manner, helping women with every day strains. The use of vaginal implants, in particular, constantly reminds us of the need for balanced, patient-centered care and watchful research eye.

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The use of implants in female pelvic floor reconstructive surgery

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Alexandridis Vasileios

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DOCTORAL DISSERTATION

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Title and subtitle: The use of implants in female pelvic floor reconstructive surgery. Short and long term efficacy and safety

Abstract:
Pelvic floor reconstructive surgery (PFRS) has suffered from high recurrence rates ever since its birth. Implants were thus quickly employed, initially autologous grafts and allografts. Technological development led to the manufacturing of synthetic implants that were believed to provide the support needed during urinary incontinence and pelvic organ prolapse (POP) surgery. However, due to a surge of reported complications, the place of implants in PFRS remains the object of major debate. Evaluation of the long-term performance of the use of implants is critical, while efforts are made for the development of new techniques, like the single-incision slings (SIS), and new materials, like the porcine small intestinal submucosa graft (PSG).

Study I is a three-year follow-up of a multicenter randomized controlled trial comparing the SIS Ajust® with conventional mid-urethral slings (MUS) for the treatment of stress urinary incontinence. Based on patient-reported outcomes, Ajust® is found to be equally effective and safe with MUS.

Studies II and III utilize a register-based cohort of women to evaluate the long-term performance of MUS for the treatment of stress urinary incontinence. Ten years after surgery, MUS demonstrate good subjective results with a small decline in efficacy and acceptable complications profile. The retropubic approach displays higher long-term efficacy than the transobturator with no difference regarding safety. No difference was found between the two techniques for the application of MUS concerning dyspareunia or pelvic pain in a ten-year perspective.

Study IV is a retrospective study examining the short-term complications and recurrence rates of POP surgery augmented with PSG. The relatively high recurrence rates do not suggest a clear benefit from PSG use, while pain and urinary tract symptoms hold a central position in the complications profile of PSG-augmented POP surgery.

In conclusion, Ajust® appears to be equally effective and safe as MUS in a three-year setting. Retropubic slings show higher efficacy than transobturator at ten years while both techniques present good results with similar and acceptable profiles regarding complications, pain and sexual function. Finally, there are no clear benefits from the use of PSG in POP surgery.

Key words: implants, mid-urethral slings, pelvic floor reconstructive surgery, pelvic organ prolapse, urinary incontinence

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Figures 2, 3, 4, 5 reprinted from: Barone WR, Abramowitch SD, Moalli PA. Chapter 13 - Host Response to Biomaterials for Pelvic Floor Reconstruction. In: Badylak SF, editor. Host Response to Biomaterials [Internet]. Oxford: Academic Press; 2015 [cited 2022 Nov 23]. p. 375–423.

Figure 6 reprinted from: Sutherland, S.E., Thompson, E.C. (2022). The Innovation of Midurethral Slings: Where We've Been and Where We Are Today. In: Cameron, A.P. (eds) Female Urinary Incontinence. Springer, Cham. https://doi-org.ludwig.lub.lu.se/10.1007/978-3-030-84352-6_16

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To Emma

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Abstract

Pelvic floor reconstructive surgery (PFRS) has suffered from high recurrence rates ever since its birth. Implants were thus quickly employed, initially autologous grafts and allografts. Technological development led to the manufacturing of synthetic implants that were believed to provide the support needed during urinary incontinence and pelvic organ prolapse (POP) surgery. However, due to a surge of reported complications, the place of implants in PFRS remains the object of major debate. Evaluation of the long-term performance of the use of implants is critical, while efforts are made for the development of new techniques, like the single-incision slings (SIS), and new materials, like the porcine small intestinal submucosa graft (PSG).

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Plain language summary

Surgery for the repair of urine leakage (incontinence) and descent of the pelvic organs through the vagina (prolapse) has displayed high risk of failure because of the weakened tissues in women's pelvic floor. In order to overcome this problem, artificial tissues (implants) were developed and used to support the descended organs, demonstrating high effectiveness. However, the emergence of serious complications related to those implants has restricted their use and has increased the need for research regarding their performance, particularly many years after surgery. At the same time, new techniques and materials are constantly developed, such as single-incision sling (SIS), which is a smaller type of sling compared to the conventional sling for the treatment of incontinence, and porcine small intestinal submucosa graft (PSG), which is a new implant material used for the treatment of prolapse.

The first study in this thesis compared a new SIS, Ajust®, with older conventional slings by randomly operating incontinent women with one or the other. This study found both slings to be equally effective and safe three years after the surgery. The second and third studies examined the performance of conventional slings ten years after the application by contacting all women known through a quality register to have received a sling in Sweden during a determined four-year period. These studies showed that conventional slings had good results for the treatment of incontinence with only a small decline in effectiveness through time and few serious complications. One of the two methods used for the application of the sling, the retropubic, displayed higher effectiveness than the other, the transobturator, with no difference in complications, sexual function or risk for pain between the two methods after ten years. The fourth study examined the performance of PSG when used for the reinforcement of women's tissues during prolapse surgery by searching the operated women's medical records. It found results similar to prolapse surgery without the use of implants but with more complications. Complications after the surgery had mainly to do with pain and urination problems.

In conclusion, the smaller Ajust® sling seems to be equally effective and safe as conventional slings after three years, the retropubic method for the application of the sling shows higher effectiveness than the transobturator with good results for both after ten years and PSG does not help significantly when used in prolapse surgery.

Populärvetenskaplig sammanfattning (Abstract in Swedish)

Kirurgi mot urinläckage (inkontinens) och framfall i underlivet (prolaps) hos kvinnor har alltid drabbats av hög risk för återfall. Vaginala inlägg (implantat) utvecklades och infördes för att förstärka kvinnornas vävnader vid inkontinens- och prolapskirurgi. De uppvisade bra resultat vad gäller effektivitet men allvarliga komplikationer rapporterades och deras bruk har begränsats. Det finns ett stort behov av mer kunskap kring användning av implantat inom inkontinens- och prolapskirurgi, särskilt rörande resultat och eventuella komplikationer lång tid efter operationen. Nya metoder och material utvecklas kontinuerligt, såsom de kortare mini-slyngorna (SIS) för inkontinensoperationer, och nya typer av implantat inom prolapskirurgi, som gris tunntarm subepitelialt implantat (PSG).

I studie I jämfördes en mini-slynga, Ajust®, med konventionella slyngor (MUS), genom att slumpmässigt lotta (randomisera) mellan de två metoderna vid operation av kvinnor med urininkontinens. Man fann att Ajust® och MUS var lika effektiva och säkra tre år efter operationen. I studie II och III granskades resultat och komplikationsförekomst tio år efter konventionell slyngoperation. De kvinnor som genomgått en slyngoperation i Sverige under en fyra-års period och var registrerade i det nationella kvalitetsregistret identifierades och fick svara på en enkät. Kvinnornas svar visade lätt minskad men ändå bra effektivitet efter tio år och få allvarliga komplikationer. En av teknikerna för applicering av slyngan, den retropubiska, uppvisade på längre sikt högre effektivitet jämfört med den transobturatoriska. Ingen skillnad rapporterades i komplikationer, sexuell funktion eller bäckensmärta efter tio år. Studie IV undersökte resultat och säkerhet vid användning av PSG vid prolapskirurgi genom granskning av opererade kvinnors journaler. Resultaten var jämförbara med vad som rapporteras vid konventionell prolapskirurgi utan implantat, men med fler komplikationer. Komplikationerna efter operationen dominerades av smärta och vattenkastningsbesvär.

Sammanfattningsvis, verkar Ajust® vara lika effektiv och säker som MUS efter tre år. Retropubisk teknik för applicering av MUS uppvisar högre effektivitet på sikt än transobturatorisk, men med bra resultat för båda efter tio år. Prolapskirurgi med PSG uppvisar inte påtagligt bättre resultat men fler komplikationer än konventionell metodik utan implantat.

List of papers

Paper I

Alexandridis V, Rudnicki M, Jakobsson U, Teleman P. Adjustable mini-sling compared with conventional mid-urethral slings in women with urinary incontinence: a 3-year follow-up of a randomized controlled trial. Int Urogynecol J. 2019 Sep;30(9):1465-1473. doi: 10.1007/s00192-019-04004-w. Epub 2019 Jun 20. PMID: 31222572; PMCID: PMC6706362.

Paper II

Alexandridis V, Lundmark Drca A, Ek M, Westergren Söderberg M, Andrada Hamer M, Teleman P. Retropubic slings are more efficient than transobturator at ten-year follow-up: a Swedish register-based study. Manuscript accepted for publication in International Urogynecology Journal.

Paper III

Lundmark Drca A, Alexandridis V, Teleman P, Andrada Hamer M, Westergren Söderberg M, Ek M. Sexual function and pain 10-14 years after insertion of a mid-urethral sling among women with stress urinary incontinence in Sweden. Manuscript.

Paper IV

Alexandridis V, Teleman P, Rudnicki M. Efficacy and safety of pelvic organ prolapse surgery with porcine small intestinal submucosa graft implantation. Eur J Obstet Gynecol Reprod Biol. 2021 Dec;267:18-22. doi: 10.1016/j.ejogrb.2021.10.011. Epub 2021 Oct 16. PMID: 34689022.

Abbreviations

ASA	American Society of Anesthesiologists physical status classification system
BMI	body mass index
CI	confidence interval
DOI	detrusor overactivity incontinence
GynOp	Swedish National Quality Register of Gynecological Surgery
HRT	hormon replacement therapy
ICD-10	International Classification of Diseases 10th Revision
ICIQ	International Consultation on Incontinence Questionnaires
ICIQ-OAB	ICIQ-Overactive Bladder
ICIQ-UI-SF	ICIQ-Urinary Incontinence-Short Form
ICS	International Continence Society
IIQ-7	Incontinence Impact Questionnaire-Short Form
IQR	interquartile range
IUGA	International Urogynecological Association
ml	milliliters
MUI	mixed urinary incontinence
MUS	mid-urethral sling
OR	odds ratio
PFRS	pelvic floor reconstructive surgery
PGI-I	Patient Global Impression of Improvement Questionnaire
PGI-S	Patient Global Impression of Severity Questionnaire
PISQ-12	Pelvic Organ Prolapse/Urinary Incontinence/Sexual Function Questionnaire
POP	pelvic organ prolapse
POP-Q	Pelvic Organ Prolapse Quantification system
PSG	porcine small intestinal submucosa graft
SD	standard deviation
SIS	single-incision sling
SUI	stress urinary incontinence
TOT	transobturator outside-in tape
TVT	tension-free vaginal tape
TVT-O	tension-free vaginal tape obturator inside-out
UDI-6	Urogenital Distress Inventory-Short Form
UI	urinary incontinence
USI	urodynamic stress incontinence
UUI	urgency urinary incontinence

Background

Urinary incontinence

Urinary continence is the complex mechanism of storage of urine in the bladder, interrupted only by the intentional disposal of urine. This function is achieved through the combined action of the central nervous system, the peripheral nervous system and organs in the pelvis (1). Sympathetic innervation, originating from the thoracic and lumbar spinal cord, results in the release of noradrenaline, which activates the inhibitory adrenergic receptors in the detrusor muscle and the excitatory adrenergic receptors in the urethra. At the same time, somatic innervation from the sacral segment of the spinal cord and via the pudendal nerve releases acetylcholine in the striated external urethral sphincter activating its contraction. Extensive connections, not yet fully understood, between the brain and the spinal cord, as well as spinal reflexes, regulate the activity of different muscles needed to preserve continence. An intact and well-functioning urothelium is also needed in order to achieve continence, both for the mechanical support it offers but also for the complex modulating functions it seems to uphold (2). Finally, the support that pelvic floor structures provide is crucial for continence, securing the correct position of the bladder, the bladder neck and the urethra during rest and activity (3). When these conditions are not fulfilled, the result can be the involuntary loss of urine, i.e. urinary incontinence (UI).

Female urinary incontinence is one of the most common morbidities for women, with around 25-45% of all women suffering from UI at some point during their lifetime (4). Around 5-15% of middle-aged and older women experience UI on daily basis (5). The way female UI is looked upon depends heavily on the social and economical background, as in many societies UI is overlooked or is considered a taboo issue (5,6). In developed countries, UI constitutes a major socioeconomic burden, with considerable practical, psychological and economical consequences, both for the individuals and the societies. It has been estimated that the annual cost for female UI in the United Kingdom exceeds 400 million pounds, of which almost half is borne by individuals (7). The corresponding cost in the USA is over 12 billion dollars with only 10% of that cost being spent on diagnosis and treatment of UI (8). Most commonly reported risk factors for UI are older age, overweight, diabetes, parity, hysterectomy, impaired physical and cognitive function, psychological disorders, family history and smoking (5).

Symptom-based allocation of women with UI in different groups has generated the most widely used classification of incontinence both within research and clinical praxis: stress urinary incontinence (SUI), urgency urinary incontinence (UUI) and mixed urinary incontinence (MUI). SUI is the complaint of involuntary loss of urine on effort or physical exertion. UUI is the complaint of involuntary loss of urine associated with urgency and MUI is the complaint of both UUI and SUI. Some other groups within this classification system are enuresis, coital UI, pregnancy associated and postpartum UI, postural UI, post-voiding UI, insensible UI, overflow UI and continuous UI (9). SUI is the most common type of incontinence, affecting approximately half of women with UI. Around one third experience MUI and a smaller portion UUI (10,11). Based on clinical findings and subsequent diagnoses, five major types of incontinence can be recognized; detrusor overactivity incontinence (DOI), urodynamic stress incontinence (USI), retention with overflow, reduced compliance incontinence, and fistula incontinence.

DOI is the result of the involuntary contraction of the detrusor muscle of the bladder and the inability to control and restrain this contraction. The pathophysiology, however, of this condition has long been debated and is often complex (12). There are both anatomical and functional factors that can contribute to the development of DOI (13). In the presence of pelvic organ prolapse, the stretch receptors that are located in the bladder wall can get regularly activated resulting in detrusor contraction. The same effect can emerge from other conditions where the stretch receptors are activated, such as tumors, pregnancy and constipation (14). The role of the bladder neck in the triggering of detrusor contraction has been debated to be more important than usually thought, as distention and passage of small amounts of urine into the proximal urethra can stimulate the micturition reflex (15). Some functional triggering factors for DOI have been identified as well. Neurodegenerative disorders, hormonal changes, chronic inflammatory diseases, infections and psychological conditions as well as plain fallacious voiding habits can lead to uncontrolled detrusor contractions (12).

USI is a diagnosis by symptom, sign, and urodynamic investigations that involves the finding of involuntary leakage during filling cystometry, associated with increased intra-abdominal pressure, in the absence of a detrusor contraction (9). Unlike DOI, USI has a more distinct anatomical background and is often associated with injury of the pubourethral ligament and the anterior vaginal wall. The result is a defective urethral support, a wider angle between bladder neck and urethra at increased intra-abdominal pressure and leakage. Intrinsic sphincter deficiency is the very weakened urethral closure mechanism, which results in low pressure in urethra and leakage of urine even at small stimuli, otherwise of no consequence (1). The common feature in both USI and intrinsic sphincter deficiency is the leakage of urine during physical activity and the therapeutic approach being the surgical effort to restore the anatomic integrity and function of the pelvic floor structures.

Although the role of anatomic changes and dysfunctions in the development of USI is generally recognized, the importance of such changes for the development of DOI has not been substantiated. Petros and Ulmsten have suggested a more anatomic-oriented view of the issue of female urinary incontinence through their integral theory, advocating the expression of all female urinary incontinence in terms of defective vaginal anatomy (3). However, such a concept has not been totally confirmed through diagnostic tools or through surgical attempts to restore the anatomy and accordingly the function of the pelvic floor. Thus, pharmaceutical approaches continue to be the focus of the attempts to help women with DOI. Many mediators have been put under a microscope in order to understand this condition and find a satisfactory answer and solution but in most cases the results are still comparable to placebo treatment (16).

Pelvic organ prolapse

Female pelvic organ prolapse (POP) is the descent of one or more of the anterior, posterior or apical parts of the vagina (after hysterectomy) or descent of the uterus/cervix. The presence of POP at examination must always be correlated with relevant symptoms, as POP itself rarely causes any health issues in the absence of subjective signs of disease. Symptoms that can be the result of POP are a feeling of pressure, fullness or pain in the pelvic area, seeing or feeling a bulge coming out of the vagina, urgency, urinary incontinence, tenesmus, bladder and bowel emptying difficulties, bleeding, atypical vaginal discharge and symptoms related to sexual activity (17). Women with uterine prolapse experience more often a feeling of pressure, while women with prolapse in the anterior and posterior compartment have in higher degree symptoms from the bladder or the bowel respectively (18,19). Some objective health issues that POP can cause are retention, ureteral obstruction, vaginal lesions and subsequent infections. The disparity between objective findings and symptoms regarding POP has led to a discrepancy of the reported epidemiology. The reported prevalence of POP is 1-31% if diagnosis is based on symptoms, 10-50% if it is based on physical examination and 20-65% if it is based on both (20). Many factors have been associated with the development of POP but older age, overweight, and vaginal birth are the most consistently reported risk factors (21). Women with POP do not seem to develop significant changes in their prolapse status over time (20).

Pelvic floor support consists of many structures the knowledge of which is important for the assessment and treatment of POP. DeLancey divided those structures into three levels; the proximal level I (cardinal and uterosacral ligaments), the middle level II (endopelvic fascia with its connections to arcus tendineus) and the distal level III (perineal body and adjacesnt muscles) (22). Although POP can be located in one of the three compartments of the vagina (anterior, middle and posterior), there are some recognizable entities in each

compartment. Prolapse of the anterior vaginal wall is the most common type of POP, present as often as the other two types combined (23,24). In the anterior compartment, cystocele is the main entity, as the descent of the urinary bladder through the weakened vesicovaginal fascia is the most common finding. However, it is not uncommon for a lateral defect of the attachment of the pubocervical fascia to the arcus tendineus fascia pelvis to be found (paravaginal defect) (25). Some authors describe this defect as much more common than usually considered, suggesting that the lateral support plays a key role for the support of the anterior vaginal wall as a whole (26). In this fashion, they highlight the significance of level II attachments for the support of the anterior vaginal wall. Moreover, imaging studies demonstrate a strong correlation between anterior wall prolapse and defect support even at levels I and III, indicating that POP, even in one compartment, is often the result of complex defects at multiple levels (27).

POP in the posterior compartment is the second most common type of prolapse (23,24). It can occur either through the protrusion of the rectum as a result of a weakened rectovaginal fascia (rectocele) or through the descent of the peritoneal sac between the vagina and the rectum, usually containing loops of small bowel (enterocele). Prolapse in the middle compartment, seen in around 5% of all women, follows mainly the impairment of the first level of pelvic support. It can also be iatrogenic due to the excision of the uterine ligaments during hysterectomy, as seen at vaginal vault prolapse (28). Both the second and the third levels of support also seem to play an important role for the development of prolapse in the posterior and the middle compartment (28,29).

Diagnostic tools

Gathering information through medical history and physical examination is the cornerstone of any diagnostic effort regarding UI and POP. When it comes to UI, there is no evidence suggesting that the use of other diagnostic tools, such as questionnaires, imaging or urodynamics, offers any advantage for the initial assessment. On the other hand, physical examination is essential, particularly for the evaluation of POP, to establish the correlation between anatomy and described symptoms and to select the most suitable treatment option. The Pelvic Organ Prolapse Quantification System (POP-Q) is a structured way to assess the type and degree of POP with easily reproducible results (30). Bladder diary, along with pad weight testing, stress test and assessment of residual urine when indicated, help to create a more objective and measurable picture of micturition habits and leakage, while testing for signs of infection can rule it out as a cause of UI (31).

The above mentioned methods can be used for the basic approach of the patient with UI and POP, while more advanced diagnostic tools can be employed in more complicated cases. Cystourethroscopy can detect a chronic inflammation in the bladder, stones, malformations in the bladder or the urethra as well as

postoperative complications, such as mesh perforation and fistulas, where even imaging tools can be useful. Imaging of the pelvic floor had previously mostly been limited to the study of the bladder and bowel. However, the increased availability of magnetic resonance imaging and especially the expanding use of ultrasound examination of the pelvic floor, has made it much easier to visualize conditions and structures of interest (31). In particular, 3D ultrasound examination offers easy access to detailed images of the muscles of the pelvic floor with many studies verifying the correlation with women's symptoms, its predictive value and its potential to engage women to pelvic floor muscle training through biofeedback (32,33). The employment of 3D ultrasound of the pelvic floor can also be helpful for the evaluation of the position of implants, especially in the case of postoperative complications (34,35). However, there is no evidence for the value of ultrasound as a routine examination regarding UI or POP. Urodynamics is another such example, with diagnostic value in selected cases but no evidence of benefit when routinely used (36,37).

Pelvic floor reconstructive surgery

Considering that POP and, to a great extent, UI are the result of weakened or injured tissues in pelvic floor, surgical efforts for the restoration of the anatomy began as early as the 16th century. It was, however, not until the second half of the 19th century that advancements in aseptic surgery, anesthetics and technology of suture materials led to considerable progress even in pelvic floor reconstructive surgery (PFRS). Amputation of the cervix and treatment of vesicovaginal fistulas were among the first urogynecological procedures performed, followed by anterior and posterior colporrhaphy, colpocleisis described by LeFort and the development of the Manchester procedure by Donald and Fothergill in the late 19th century. It was already clearly advocated that the removal of the uterus was not necessary but instead it could be used for the anchoring of adjacent structures.

During the 20th century, the development of new surgical procedures was accelerated assisted by the use of antibiotics and the way most medical conditions were treated changed radically. PFRS was part of this revolution as new techniques and instruments constantly emerged. At first, the round ligaments were employed for the suspension of the uterus followed by the use of uterosacral ligaments and the plication of cul-de-sac for the treatment and prevention of enterocele. The paravaginal repair for lateral anterior wall defects was described in the early 20th century, the procedure of vaginal hysterectomy was standardized and McCall described his culdoplasty using the uterosacral ligaments to obliterate the cul-de-sac. Abdominal approaches for the management of POP were introduced employing a variety of techniques, mainly for apical prolapse. Sacral hysteropexy without the use of mesh was introduced in the 50's, while vaginal sacrospinous fixation was developed in the 70's, as did the site-specific rectocele repair.

The plication applied at the urethrovesical junction as described by Kelly in the 1910's was the first attempt to support the urethra in order to treat SUI. The long-term results, however, were not satisfying when only vaginal tissue was used. Various techniques were tested, using adjacent structures to support the urethra. In the 40's, Aldridge developed an approach through suprapubic incision in order to create fascia strips that were brought through the rectus muscle under the urethra and were connected there as a sling. Abdominal approaches for the suspension of the urethrovesical junction were developed in the middle of the 20th century, first to the retropubic peritoneum by Marshall, Marchetti and Krantz and later to the Cooper's ligaments by Burch. Those techniques had acceptable success rates but relatively high morbidity. Pereyra tried to overcome this problem by developing a needle suspension of the urethra to the rectus fascia but this resulted to lower efficacy. McGuire and Lytton presented their results using the pubovaginal sling procedure in the 70's, combining acceptable efficacy and complications profile after applying an autologous rectus fascia sling under the urethra (38–46).

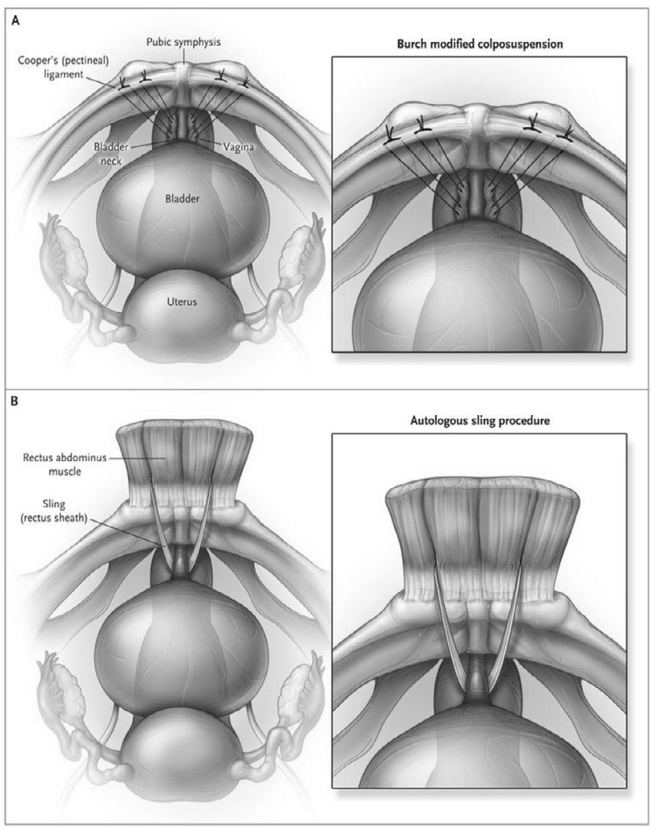

Figure 1. Burch colposuspension and autologous sling procedure. Reproduced with permission from Massachusetts Medical Society

Implants

Terminology

The following terminology was suggested by the Standardization and Terminology Committees of the International Urogynecological Association (IUGA) and the International Continence Society (ICS) and the Joint IUGA/ICS Working Group on Complications Terminology (47):

Implant: a surgically inserted or embedded prosthesis.

Mesh: a (prosthetic) network fabric or structure; open spaces or interstices between the strands of the net. The use of this term would be for prolapse surgery with synthetic materials.

Graft: any tissue or organ for transplantation. This term will be used to refer to biological materials inserted.

a. Autologous grafts: from patient's own tissues, for example, dura mater, rectus sheath or fascia lata.

b. Allografts: from post-mortem tissue banks.

c. Xenografts: from other species, for example, modified porcine dermis, porcine small intestine and bovine pericardium.

Tape (Sling): a flat strip of synthetic material. The use of this term would be for incontinence surgery with synthetic materials.

History

The results of the advancements in PFRS during the 20th century were life-changing for many women but soon it became obvious that in some cases the native tissue repairs could not offer a solution in the long run and recurrences were difficult to deal with. Efforts to find a suitable prosthetic implant in order to reinforce native tissue hernia repairs were made before the end of the 19th century with poor results. Surgeons assumed that the main problem was the multifilament suture materials that were used, mainly silk and cotton. It was, though, not until the 50's when Usher experimented using different polymers and found that a woven polyethylene mesh (Marlex) displayed some very good properties. Further research led to the advantageous knitted polypropylene mesh that was, however, not widely used before the 80's.

Shortly after its evaluation within hernia repairs, the Marlex mesh was also introduced in PFRS. This was done by Lane who described in 1962 a sacrocolpopexy with mesh for vaginal vault prolapse. However, it was only after the development of the retropubic (RP) sling by Petros and Ulmsten in the 90's that the

use of mesh was extensively used in vaginal prolapse and incontinence surgery. The first efforts were made with polyethylene mesh tapes (Mersilene), resulting in high erosion rates, but the use of knitted polypropylene mesh solved this problem. Afterwards, surgeons started to employ implants in POP surgery, starting from the anterior compartment for the treatment of recurrence and gradually extending its use in the other compartments and even in primary surgery. This was done assuming that the low complications rates of sling surgery for incontinence would be sustained when mesh would be used for prolapse repair. However, this was not the case and a large number of women with mesh-related complications started to emerge. Efforts to find absorbable materials, mostly biological grafts, in order to minimize the risk for complications did not pay off, as their long-term efficacy was not substantiated. The use of mesh in prolapse and partially even in incontinence surgery was restricted following massive lawsuits and resulting in ongoing debate regarding their place in PFRS (38,40,42,43,45,48–55).

Biocompatibility

The goal with every implant within PFRS is to integrate or dissolve into the host's tissues, leaving behind a structure of long-lasting effect but no long-term inflammation, no allergic reaction, no risk of transmitting an infection, be non-carcinogenic, resistant to infection, keep its mechanical properties and at the same time be easy to handle and accessible cost-wise (50,53). Designing the ideal implant material is a complex procedure during which all the above must be considered. The element, though, that has especially drawn the attention of researchers is the healing process that follows the insertion of any implant. This process has some stages the development of which is directly associated to the properties of the implant and can determine the final outcome of the procedure (56).

The first reaction towards an implant is the adhesion of proteins and platelets around the foreign body that creates a matrix. Even at this early stage of reaction, the type of the implanted material can affect the composition of this matrix. Through chemotaxis, neutrophils and other cells are recruited to the site as a first acute inflammatory response within some hours. This might be adequate regarding microorganisms but in the case of implants the reaction progresses to a chronic inflammation, during which monocytes differentiate into macrophages in an effort to discard larger substances. Not being able to do so, the next step is a foreign body reaction with the formation of giant cells within some days from the implantation. Even when they are not able of phagocytosing the foreign body, as in the case of implants, those giant cells secret factors in order to degrade it and phagocytose the smaller fragments. This is the acute foreign body reaction during which the absorbable implants dissolve leaving behind remodeled tissue with the help of fibroblasts and neo-capillaries (57). The speed of absorption during this stage can affect the outcomes of the surgery with absorbable implant. A degredation that takes place too early can affect the efficacy negatively, while a

too late one can cause chronic inflammation and postoperative complications. When non-absorbable implants are used, foreign body reaction continues to a chronic phase that ends, like in the case of absorbable implants, with the formation of a scar (fibrotic phase). However, in this case the fibrotic capsule surrounds the implant, usually within two weeks. Fibroblasts reach then their highest levels depositing collagen and, along with other cells and neovascularization, they continue the remodeling of the scar tissue and its strengthening that takes place over the course of months (50).

An adequate inflammatory foreign body reaction is essential for the integration/dissolvement of the implant but the balance in that reaction is crucial. A more aggressive reaction can lead to chronic inflammation, forming a stiff scar plate with subsequent shrinkage, deformation, poor adherence, infection and ultimately pain, recurrence, erosion or rejection. After the inflammatory response and during the fibrotic and remodeling phase, the composition and arrangement of the new scar tissue can also drastically affect the outcomes of the surgical procedure. These outcomes are to a great extent determined by the properties of the implant used (53). The pursuit of the ideal implant in reconstructive surgery has led to the development of many different types of implants with different properties. The knowledge of those properties is essential when a clinical choice for the use of an implant is made, as certain properties are associated with certain outcomes.

Properties of implants (50,53,54,58–60)

Absorption

Implant materials are either absorbable or not. An implant can also be a combination of absorbable and non-absorbable materials. Even when an implant is absorbable, the speed with which it dissolves varies and depends not only on the material used but also on the other properties of the implant. In general, non-absorbable implants are associated with high efficacy but at the same time high risk for complications, whereas absorbable implants display better complications profile but worse long-term efficacy.

Weight

The weight of an implant, and more precisely the weight per unit area, depends both on the material used and the construction of the implant. Heavyweight meshes display higher resistance to forces but lightweight meshes are associated with lighter inflammatory reaction, less collagen formation and better complications profile. This can though be the result of the larger pores that lightweight meshes are typically constructed with.

Constitution

When yarn is used for the construction of an implant, it can be either monofilament or multifilament. Monofilament implants are strong but stiff and, although multifilament implants are more pliable, the risk for infection is higher, as the small spaces that are formed between multifilament yarns promote bacterial growth. Coated implants have been developed using a variety of substances in order to modify their properties.

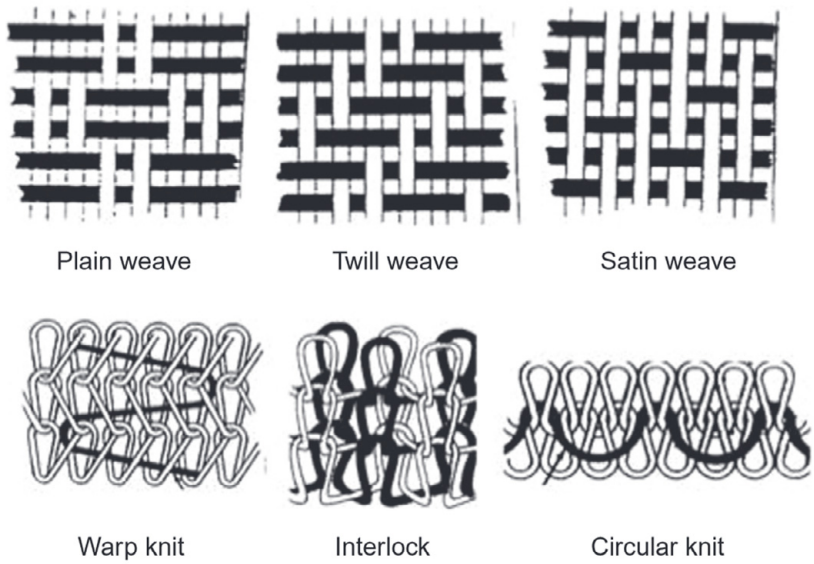

Figure 2. Various types of weave (top) and knit patterns (bottom) can be used to construct synthetic mesh products. Reproduced with permission from Elsevier

Structure

The textile structure of implants is very important for their behavior when implanted. Non-woven (created through other methods of bonding) and woven structures are rarely used for the construction of meshes. Knitted structures have mechanical advantages offering elasticity but also better biocompatibility, through the large pores created. The warp-knitted implants in particular are even more elastic and can be trimmed maintaining their structure. Cross-linked xenografts are more resistant to degradation than non-cross-linked which demonstrate greater cell infiltration and degradation but also lower risk for long-term complications.

Pore size

Large pores in meshes (commonly >75μm) result in better biocompatibility as they assist the access of macrophages and fibroblasts, allowing for the formation of

connective tissue between the mesh structures without encapsulating the whole mesh. In this way, infections are prevented, integration is optimized and the mechanical properties of the mesh are sustained. The ideal pore size may differ depending on the material used and even the shape of the pores may affect the clinical outcomes. Microporous meshes are usually considered those with pores <10μm while submicronic pores are those <1μm.

Tensile strength and elasticity

Tensile strength is the maximum force that can be applied to an implant without breaking it. Elasticity is the maximum distension of an implant under a force, being able to recover its original form after the force has been withdrawn. Heavyweight meshes display higher tensile strength but most lightweight implants display adequate tensile strength in vitro and in vivo for the pelvic floor being at the same time more elastic.

Classification

There is currently no widely used classification method for implants within PFRS. Most often implants are divided into groups based on the separate properties that are of interest on each occasion. A chronological classification approach divides the implants into three groups (50,53,54):

First generation implants are mostly non-absorbable meshes constructed from polymers, such as polypropylene, polyethylene, polytetrafluoroethylene and expanded polytetrafluoroethylene. In this group there are, however, even some absorbable multifilament meshes constructed from polyglactin or polyglycolic acid. First generation implants are further divided into type I meshes (macroporous and monofilament), type II (microporous), type III (macroporous with microporous or multifilament components) and type IV (coated meshes with submicronic pores). First generation meshes are still the most widely used within PFRS, which is indicative of the low-grade advancements in this field.

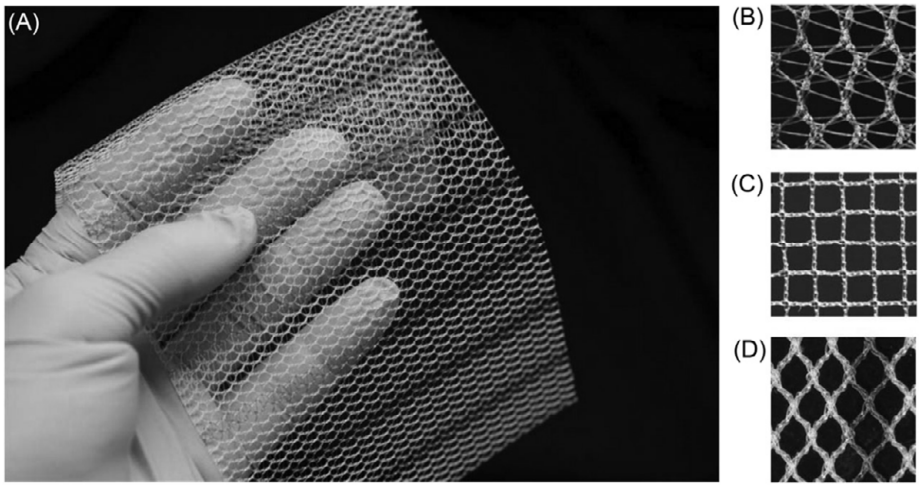

Figure 3. Gynemesh PS (A,B), Restorelle (C), and UltraPro (D) are all examples of knitted, Type I, polypropylene, macroporous mesh, despite a wide range of pore architectures. Reproduced with permission from Elsevier

Second generation implants were developed primarily for intraperitoneal application. They are constructed from a combination of materials in order to minimize undesired adhesion to neighboring surfaces as each side consists of a different material. Such materials used are titanium, omega 3, collagen, cellulose, poliglecaprone 25 and polyvinylidene fluoride, usually in combination with polymers from the first generation meshes.

Third generation implants were the result of concerns raised over non-absorbable meshes and reported complications. Biologic materials were developed for the construction of scaffolds and many different sources were employed. Autologous grafts and allografts had already been used but various xenografts were now produced. Scaffolds from dermis, small intestinal submucosa and pericardium of mostly porcine and bovine origin are decellularized and sterilized to only leave collagen that acts as a matrix for the creation of new connective tissue.

Future perspective

The perfect implant for use within PFRS is yet to be developed. Progress has taken place both regarding the understanding of the particular conditions present in pelvic floor and the separate properties of implants that are required but also regarding the actual development of better implants and surgical techniques. New instruments for easier, more effective and less traumatic insertion of implants have been designed and continue to evolve (53). One field that demonstrates notable advancements is the development of new materials for the construction of implants. Many different kinds of coatings and combinations of different materials

have been tested in order to enhance the mechanical and biological characteristics with promising in vitro and in vivo results. Nanofibers, with various innovative methods of production, improve cell adhesion and infiltration while at the same time offering high commercial availability. Mesenchymal stem cells and differentiated cells combined with absorbable meshes can reduce the foreign body reaction and promote tissue integration and regeneration. The addition of growth factors and hormones seem to improve cell proliferation and differentiation while antibiotics have been tested in order to reduce the risk for infections (50,61–63).

Pelvic floor reconstructive surgery using implants

The use of implants in PFRS demonstrates some particularities that make it differ from their use in their most common field of application, i.e. hernia surgery. One major difference is that PFRS is performed near the vagina, that is heavily colonized with bacteria, and infection can result in extensive inflammation, pain, rejection or extrusion (58,64). The fact that the risk for extrusion is significantly higher when a vaginal incision/vaginal manipulations are done together with the application of an implant or when that incision is larger (POP vs. sling surgery), is indicative of the important role of the vaginal environment for the outcome of the surgery (65,66). Moreover, implants in hernia repair are in contact with fascia but within PFRS the implant is also in contact with other tissues, such as muscles, the bladder or the rectum, which can affect its biocompatibility and its complications profile.

One other important factor that affects the performance of implants is the forces applied on it. In contrast to the multiaxial forces on the implants when implanted for hernia repairs, the forces in the case of PFRS are usually uniaxial, as the supporting structures aim primarily to suspend. Additionally, the points of attachment are fewer and not as spread as they are when implants are used in hernia surgery, while in PFRS the implants fold at greater extent. The result of all the above is that the size of the pores is much easier to decrease, which affects the properties of the implant drastically. Thus, even the geometry of the pores and their orientation in relation to the forces applied must be taken into account when an implant is designed and selected for a specific site or type of POP in order to minimize the effect on the pore size (58). At a more advanced level, the choice of implant and its orientation in the operation site could be personalized for each patient as a means of minimizing the risks and optimizing the efficacy.

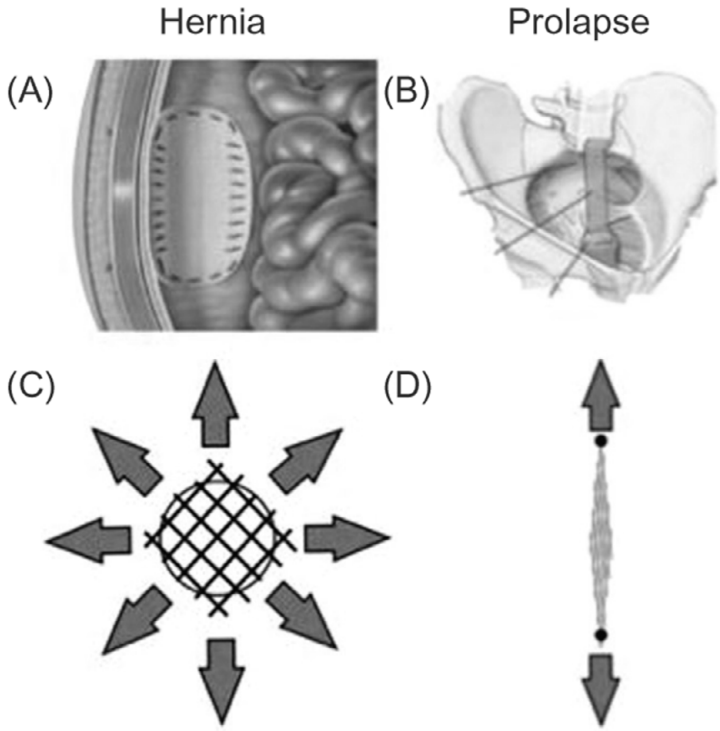

Figure 4. The site of implantation dictates the mechanical environment a mesh experiences. For hernia repair, mesh is implanted in the abdominal wall via sutures along the entire boundary (A and C). This loads all the axes of the mesh simultaneously. For prolapse repair, mesh is loaded in a predominately uniaxial fashion (B and D). Uniaxial loading is more likely to result in collapse of mesh pores. Reproduced with permission from Elsevier

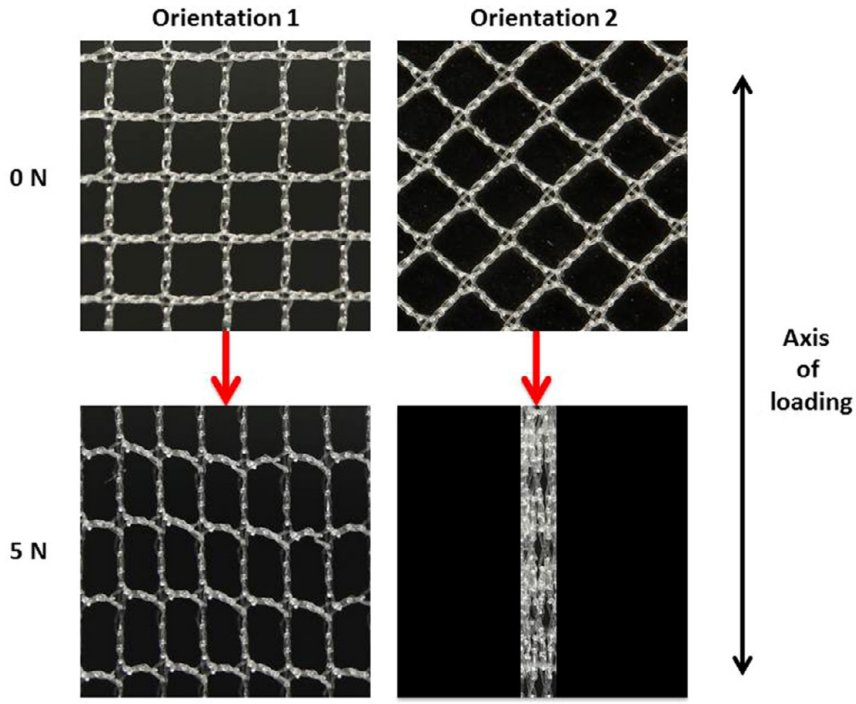

Figure 5. The deformation of mesh under uniaxial loading is highly dependent on the mesh orientation relative to the axis of loading. Reproduced with permission from Elsevier

Higher levels of concentrated loads lead to higher levels of stress in the tissues. Stress has been shown to increase fibroblast activity leading to stronger inflammation and higher risk for contraction and extrusion. In the case of grafts, inflammation increases the speed of absorption and absorbable implants have been shown to degrade at higher extent near the vaginal environment. All the above together with the impact of hormones on the healing process demonstrate the many particularities regarding the use of implants in PFRS (58).

Urinary incontinence

The concept of providing support to the urethra using an implant in order to cure UI is old and the use of autologous grafts for UI was the first application of implants within PFRS (38). It was also the development of the RP polypropylene mid-urethral sling (MUS) by Ulmsten and its success that led to the wide use of implants even for POP. That same RP MUS is still considered to be the gold standard for the treatment of SUI (31,67,68). The sling is placed under the mid-urethra using an incision in the anterior vaginal wall, passes through the urogenital diaphragm, laterally to the bladder on each side, behind the pubic bone and exits

through the skin. The transobturator (TO) approach for the insertion of the sling was later developed in order to minimize the risk for bladder injury. The sling is instead led laterally through the obturator foramen and exits through the skin between the vulva and the thigh. Both techniques present high efficacy, with short-term subjective cure rate between 62% and 98% and long-term between 43% and 92% (69). The RP technique in particular is the one studied under the longer period of time with data from longer than 15-year follow-up studies showing a small decline in efficacy and acceptable complications profile (70–72). The risk for adverse events is low with both techniques but the RP approach demonstrates worse complications profile, as higher risk for retention, bladder and vascular injury is reported. On the other hand, higher risk for groin pain is reported after the TO approach and higher risk for reoperation because of recurrence. The risk for exposure is around 2% for both techniques and sling-related reoperation rates range from 0.8% to 2.4% (69,73–75). Those numbers do not change significantly in long-term follow-up studies but potential sling-related complications, such as UUI, voiding difficulties, pain and dyspareunia that are relatively common in older women, are difficult to assess and attribute to the implant or not.

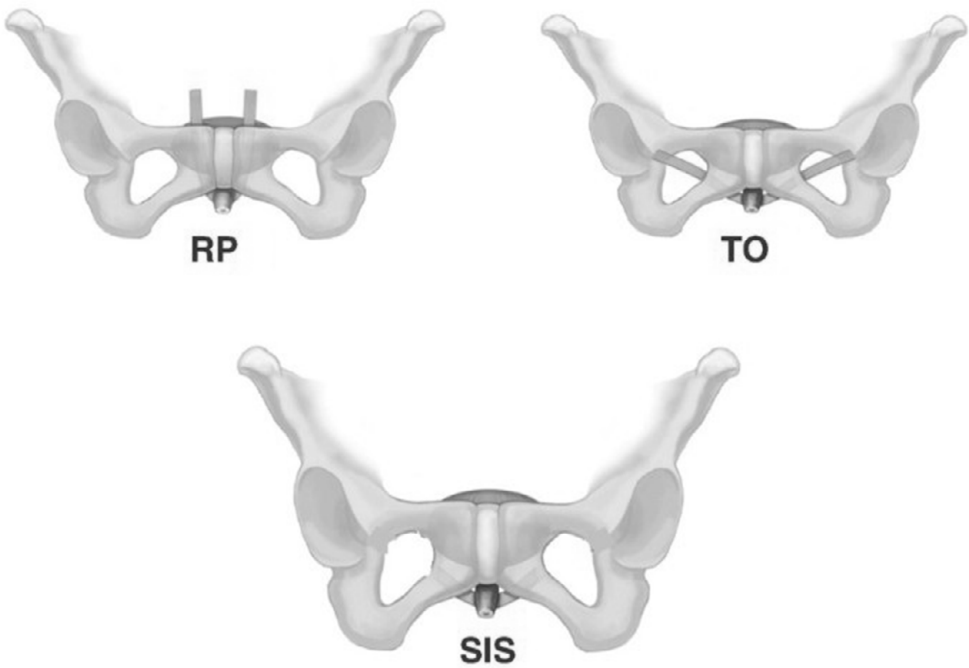

Figure 6. Retropubic (RP), transobturator (TO) and single-incicion sling (SIS). Reproduced with permission from Elsevier

In particular, the potential effect of MUS on bladder emptying and the risk for voiding difficulties are not fully understood. MUS display actually a cure rate of around 30-85% regarding urgency and UUI on top of their effect on SUI (76) but the pathophysiology behind this finding has not been clarified. As perceived by Petros and Ulmsten, MUS was designed to replace the damaged pubourethral ligament and support the urethra in situations associated with effort with no tension applied during rest. However, urodynamic studies conducted on women having received a pubovaginal sling showed a significant increase in detrusor pressure at maximum urinary flow rate in women with successful outcome after the surgery, indicating a positive association between outlet obstruction and efficacy of the treatment (77). This is supported even by imaging studies that demonstrate that urethral kinking can occur in women with MUS as only the mid-urethra is supported while the most proximal and distal parts of the urethra follow the weakened anterior vaginal wall (78). Moreover, higher rates of kinking have been recorded after the RP approach compared to TO (79), while at the same time the RP approach displays both higher long-term cure rates and higher rates of retention (67,75). The exact mechanism for these effects is unclear but, even in the integral theory, the significance of the weakened vagina as a whole for the development of SUI and not only the role of the pubourethral ligament is highlighted. There are currently no data on the effect of anterior vaginal/ paravaginal repair plus urethral support (e.g. Kelly sutures) compared to MUS for the treatment of SUI or UUI (69).

Recently, single-incision slings (SIS) were introduced, where the sling is anchored to the obturator membrane instead of exiting through the groin. The efficacy of this technique seems to strongly depend on the fixation mechanism but when it is adequate, the short- and medium-term results are comparable to other MUS. However, no substantial advantage has yet been demonstrated with SIS (80). Some absorbable sling materials have also been used, not gaining much popularity due to higher morbidity at the site of extraction in the case of autologous grafts, higher costs in the case of xenografts and signs of worse long-term efficacy (67,81). Their use, though, has lately necessarily become attractive in some countries due to restrictions in the application of meshes.

Pelvic organ prolapse

The use of implants in POP surgery has been the most debated issue in urogynecology and consensus is still not reached (55). It can be divided into two groups; vaginal and abdominal surgery.

Vaginal surgery

The vaginal use of implants was developed in order to deal with the high recurrence rates that are observed with native tissue repairs. The most common site of application has been the anterior compartment where recurrence is seen in

more than 30% of native tissue colporrhaphies (82). There is a plethora of techniques used and structures described for the attachment of implants when inserted vaginally; free application, suturing to the plicated fascia, the arcus tendineus fascia pelvis, the uterosacral ligaments, the perineal body, the urogenital diaphragm or suspension to the sacrospinous ligament, the obturator membrane and the iliococcygeous muscle. The evaluation of the efficacy of implants has been to some degree encumbered by the diversity of the techniques used.

Absorbable meshes and biological grafts possibly offer better objective outcome in the anterior compartment compared to native tissue repair but no difference has been demonstrated regarding subjective efficacy for the women or repeated surgery for prolapse, while at the same time the complications rate is higher. Non-absorbable meshes have shown good results in the anterior compartment with recurrence rate of approximately 13% but at the same time exposure rate of approximately 11% (83). There is lack of evidence concerning the use of mesh in the posterior compartment and data concerning the middle compartment do not support the vaginal use of mesh (84,85). Looking at several reviews, the efficacy of surgery with mesh in the anterior compartment seems to undoubtedly be higher than native tissue repairs (25,83,86). The extent though to which this is true should be evaluated cautiously as in many comparing studies the technique used differs between the two groups in more aspects than just the application of the mesh. More extended approaches are sometimes employed for the attachment of the mesh that can per se affect the result. Moreover, many studies, some without being blinded for the examining physician, focus on objective outcomes and not on the far more important subjective results for the women. One characteristic example is that of the large multicenter randomized PROSPECT study that could not demonstrate any benefits from the enhancement of colporrhaphies with xenograft or mesh regarding subjective outcomes up to six years postoperatively. No difference was recorded regarding dyspareunia or pain either but more than 8% of the women that received a mesh had repeated surgery due to mesh complications (87).

Abdominal surgery

The abdominal use of implants in PFRS is predominated by the sacral colpopexy or the sacral hysteropexy. This procedure, where an implant is used to suspend the vagina or the uterus to the sacral periosteum, is considered by many to be the gold standard for the surgical treatment of apical prolapse (88,89). The use of mesh has demonstrated better results than absorbable materials but the evidence regarding the superiority of this procedure over other vaginal or abdominal approaches is at least weak (90). In a Cochrane review from 2016, when awareness of prolapse was examined, only three studies that compared different techniques to sacral colpopexy or hysteropexy were analyzed and they did not demonstrate any significant difference, not even when results from studies with the same technique were pooled together. Only when all those different studies were treated as the same intervention, was it possible to find significant difference in awareness of

prolapse (85). There are many variations of the sacral colpopexy described and other structures for the abdominal attachment of the implant have been suggested but none of these approaches has been put under further research scrutiny.

Efficacy and safety

The two main issues with the use of implants in PFRS are whether they can offer any advantage compared to native tissue repairs and if that advantage is worth the risk having a complication caused by their use. This is by all means something that needs to be answered by the woman herself but an informed decision needs to be grounded on evidence-based knowledge.

Regarding surgery for UI, the benefits from the use of implants are established through long-term follow-up studies that show better results compared to native tissue colposuspension and even lower morbidity (67,91–93). The subjective cure rates recorded are over 80% in short-term follow-up studies and around 70% in long-term, while the satisfaction rates are around 90% (67,69,75,80,81,92,93). There is, though, higher risk for voiding difficulties associated with the use of implants and risk for exposure. The type of implant used varies, with polypropylene mesh having the advantages of the minimal invasive procedure and durability but exposure rates of approximately 2%, while autologous grafts avoid the risk for mesh-related adverse events. There is some evidence for the RP approach to perform better than the TO in the long run with much lower risk for groin pain but the TO approach records lower rates of retention and perioperative adverse events (69,75,92). It is, however, unclear if those adverse events have any impact on women's long-term experience. The use of absorbable meshes and xenografts is not well documented. One more aspect that is not adequately explored is the impact of implant use on urgency, voiding difficulties, chronic pain and sexual activity. This is though difficult to assess as there are no randomized trials comparing the use of implants with conservative management. However, data from studies with short- to medium-term follow-up show that the incidence of de novo or worsened urgency and urgency incontinence is around 9%, the incidence of voiding dysfunction 6% and chronic pain 5% (67,69,74). Sexual function seems to improve after surgery with MUS (94–103), while the risk for de novo dyspareunia is low, around 1-2% (69). Studies with long-term follow-up present difficulties in the assessment of such subjective outcomes, as it is difficult to distinguish between sling- and age-related conditions.

The use of implants in POP surgery displays some characteristics that render it much different than that for UI. Firstly, its advantages compared to native tissue repairs are not well established, as explained above. Secondly, the complications profile of meshes used within POP surgery are very different. In contrast to the small slings inserted for the treatment of UI, the enhancement of POP surgery employs large implants which, when applied vaginally, require large vaginal incisions. Therefore, the risk for exposure is much higher and rates around 11%

for vaginal procedures. This is, however, the only complication that can without any doubt be attributed to the use of implants. There is, actually, no evidence that the enhancement of a POP repair with an implant leads to higher risk for pain, dyspareunia or any urinary symptoms (83–85,104).

The key point regarding the use of implants in PFRS is that rigorous evaluation of the possible advantages and disadvantages of their employment is crucial preoperatively. The available options for dealing with the problem without using an implant should be considered and only after an informed decision made by the woman herself should an implant be applied. It is important not to group together all implants and all procedures and treat them as one considering the inherent differences between conditions, materials and techniques.

Rationale for the thesis

The use of implants in PFRS is a subject of constant controversy. There is little that is considered to be fully known and the concluding message of reviews in almost every field is the need for studies, especially with long-term follow-up. In particular, SIS have been recently developed and there is still uncertainty regarding their place in the treatment of female SUI. Seven studies have been found (105–111) to compare the long-term (≥ 3 years) performance of SIS and MUS. There are signs of worse objective cure rate for the SIS, not confirmed by all the meta-analyses that have been performed. No difference has been found in subjective outcomes and SIS seem to have better perioperative complications profile and may be more cost effective (80,112–114). Ajust® is a SIS that has the theoretical benefit of the ability to modify the tension of the sling during the application, in contrast to most other available SIS, which have a fixed length. Moreover, the fixation system of Ajust® has been found to better attach to the obturator complex when compared to other SIS (115). This is particularly important with respect to the significance of fixation systems for the performance of SIS. TVT-Secur, a SIS withdrawn from the market, had consistently demonstrated inferior results compared to conventional MUS, which is generally accepted to be due to the failure of its fixation system (116,117). There are, however, no data on the long-term performance of Ajust®, as the follow-up period of studies evaluating Ajust® is limited to one-two years (118–131).

On the other hand, MUS have been the object of research studies during a long period since their introduction in the 90's. Currently, both the RP and the TO technique for the insertion of the sling are used as they both display some advantages. The most distinct differences noted concern the complications profile of the two approaches, mostly perioperatively, i.e. higher risk for bladder injury, bleeding and retention with the RP technique and higher risk for groin pain with the TO. It is still unclear if there are any differences regarding the long-term complications profile (69,75). Specifically, voiding difficulties, pain and dyspareunia are three aspects of the MUS profile that studies with long-term follow-up have not had their focus on. The accumulation of data from medium- and long-term studies during the decades that MUS have been used has shown signs of superiority of RP slings with regard to long-term efficacy (132–136), which some reviews also have reported (67,75). This is though not confirmed by all performed meta-analyses. Such knowledge has become increasingly important, especially with respect to the ageing population.

Finally, the search for the ideal implant within PFRS continues and xenografts seem to be promising materials, combining absorbability and durability (137). Despite these high expectations, potential advantages of their use in clinical praxis have not been substantiated (83–85). There is, however, evidence of significant heterogeneity in the performance of the various xenografts, which does not allow treating them as a homogenous group (138). Specifically, PSG displays very good in vitro and in vivo properties compared to other grafts (139,140). There are a few comparing trials evaluating the enhancement of anterior and posterior prolapse repair with PSG, which have not been able to show any benefits from its use (141–143), and some case series with a small number of patients have not focused on the complications profile of PSG use (144,145).

Objectives

Study I

The aim of this study is to compare the subjective long-term performance of surgery using a SIS (Ajust®) with conventional MUS for the treatment of SUI in women. The primary objective is to compare the patient-reported cure rate between the two techniques three years after the application of the sling. Secondary objectives are to compare the patient-reported improvement, complications and symptoms regarding urinary incontinence and pelvic floor function.

Study II

The aim of this study is to examine the subjective long-term efficacy and safety of MUS and compare the RP and TO techniques for the insertion of the sling. The primary objective is to measure the patient-reported cure rate of MUS ten years after the application and compare the two techniques used. The secondary objective is to estimate the frequency of mesh-related complications as reported by the women and evaluate their nature.

Study III

The aim of this study is to evaluate MUS regarding the long-term impact of their use on pain and sexual function. The primary objective is to compare sexual function and prevalence of pelvic pain between women having received a RP and a TO sling ten years before. Secondary objectives are to compare the two techniques regarding coital incontinence, feeling of vaginal tightness and PISQ-12 scores.

Study IV

The aim of this study is to evaluate the efficacy and safety of PSG use in POP surgery. The primary objective is to estimate the percentage of women developing a POP-Q stage ≥ 2 in a compartment operated with PSG at three-month follow-up.

Secondary objectives are to evaluate the complications profile of PSG-augmented POP surgery and identify potential risk factors for the manifestation of complications and recurrence of prolapse.

Materials and methods

Study I

This study is a three-year follow-up of a multicenter randomized controlled trial comparing Ajust® with conventional MUS. Between May 2012 and April 2014 women from eight centers in three Nordic countries were randomly allocated to either receive an Ajust® (Bard, Murray Hill, NJ, USA) or one of the following MUS: tension-free vaginal tape (TVT) (Ethicon, Somerville, NJ, USA), TVT-obturator inside-out (TVT-O) (Ethicon Inc) or transobturator outside-in tape (TOT) (Monarc, AMS, MN, USA). The choice of the type of MUS applied was done according to the preference of each of the eight centers in Denmark, Norway and Sweden that participated. Randomization was carried out through a computer-generated list in blocks of 25 corresponding to each center in a ratio of 1:1 to either Ajust® or MUS. A random allocation sequence was generated by an independent statistician and sealed, non-transparent envelopes were used during randomization. Data were recorded following inclusion.

All women received oral and written information about the study and written consent was acquired before inclusion. Included women had SUI or MUI with predominant SUI. SUI was confirmed with a positive stress test (cough test) after the bladder was filled with 300 ml water. Preoperative assessment included medical history and physical examination. All women had either tested pelvic floor muscle training and failed with regard to improvement of symptoms or had declined it. Exclusion criteria were women older than 60 years of age, MUI with predominant UUI, POP of stage ≥ 2 at examination, previous UI or POP surgery, planned or present pregnancy, residual urine volume > 100 ml, previous pelvic irradiation, repeated urinary tract infections (four or more during the previous year), neurological conditions such as multiple sclerosis, current treatment with corticoids, inability to understand the protocol and a history of genital or abdominal cancer or a pelvic mass.

All surgeons performing the insertion of the slings were specialized gynecologists that had performed more than 100 MUS applications and at least two applications of Ajust® under the instructions of a trained supervisor before participating in the study. The participating women received local, spinal or general anesthesia according to the regimen of each clinic and the specific needs of each woman, as they would otherwise be treated at each center. Cystoscopy was performed perioperatively in all cases after the insertion of the sling.

In total, 305 women were included in the study; 155 received Ajust® and 150 received a MUS. Of those, 83 received TVT, 13 TVT-O and 54 TOT. One-year follow-up was carried out with 280 women participating; 141 in the Ajust® group and 139 in the MUS group. At one-year follow-up, both the objective and subjective performance of Ajust® was evaluated and no difference was found compared to MUS (146). Seven of the eight centers that initially participated in the study participated even at three-year follow-up, one not being able to participate due to local logistics issues. All women (from the seven centers) that participated in the one-year follow-up were contacted at least three years after the application of the sling in order to participate in the three-year follow-up. They received letters with information about the study and questionnaires to fill out. Women that did not respond were contacted with letters one more time before exclusion.

The choice of the questionnaires that were used at three-year follow-up was dictated by the ones used at one-year follow-up in order to facilitate comparison. They were in agreement with the International Consultation on Incontinence and the International Urogynecological Association recommendations for the evaluation of urinary incontinence and pelvic floor function in women (147,148). The International Consultation on Incontinence Questionnaires (ICIQ), Urinary Incontinence-Short Form (ICIQ-UI-SF) and Overactive Bladder (ICIQ-OAB), the Patient Global Impression of Improvement (PGI-I) and the Patient Global Impression of Severity (PGI-S) questionnaires and, if sexually active, the Pelvic Organ Prolapse/Urinary Incontinence/Sexual Function Questionnaire (PISQ-12) were used together with a two-day bladder diary for the evaluation of the effect of the procedures on the women's urinary tract symptoms and pelvic floor function in addition to quality of life parameters. All questionnaires used are validated (148–150), while the PGI-I and PGI-S questionnaires are also validated in women with SUI (151) and the PISQ-12 questionnaire is also validated in its Swedish version (152).

The study was designed as a randomized trial and one-sided power analysis that was conducted before randomization showed that the inclusion of 131 women was required in each arm anticipating a cure rate of not less than 9% for Ajust® compared with MUS (α=0.05, β=0.2). Data were analyzed using descriptive and analytical statistics. When analyzing descriptive data, mean, standard deviation, and range were used for continuous data, whereas median, interquartile range, and frequencies (n and percentage) were used for ordinal and nominal data. Student's t test was used for normally distributed data and, for ordinal and non-normally distributed data, the Mann–Whitney U test or the Friedman test was used for comparison between groups. Post-hoc analysis of the Friedman test results was conducted using the Wilcoxon signed-rank test with a correction applied using the Bonferroni method (α=0.017). The Chi-squared test and Fisher's exact test were used for nominal data. All analyses were performed using IBM SPSS Statistics 24 and the statistical significance was set at < 0.05 (except for the post-hoc tests).

Study II & III

This study was initially designed as a project to be carried out by our study group at Lund University, Sweden. When the study protocol was written and the application for ethical approval was prepared, we were mutually informed that another study group, in our case from Karolinska Institute, Stockholm, Sweden, was preparing a similar project with similar study population. The two study groups came in contact and developed a common study protocol with extended objectives and shared domains of responsibility.

The study was designed as a register-based cohort study with ten-year follow-up of women that received MUS in Sweden. The Swedish National Quality Register of Gynecological Surgery (GynOp) was employed in order to find women that were operated upon with MUS in Sweden between 2006 and 2010. GynOp was designed as a tool to facilitate potential future research and contains a wide range of preoperative characteristics of the registered women, along with information regarding surgery, perioperative period, hospital stay and status at discharge. Postoperative follow-up information carried out through GynOp is recorded on two occasions: after two months and after one year, both with questionnaires answered by women and an evaluation of the answers done by a physician. There are no data about the coverage rate of GynOp concerning incontinence surgery in Sweden during the study period but during the following four years, this rate was between 85% and 90% (153).

All the variables that were available in GynOp were examined to find those we wished to use in order to extract information about the eligible women in the study. The chosen variables were those related to the women's contact information, baseline characteristics, surgery information, perioperative and postoperative complications as well as one-year outcomes regarding efficacy, sling-related symptoms and reoperations. In collaboration with GynOp, the data of the women that were operated with MUS between 2006 and 2010 were extracted. If contact information was missing, it was recovered using the Swedish Tax Agency database. All women that were operated upon with a MUS during the study period were included, irrespective of type of incontinence, possible concomitant surgery, previous prolapse surgery or incontinence surgery or previous use of vaginal implant. Women operated upon with a MUS more than once during the study period were also included, and the GynOp data from the first surgery were used. Women were excluded if an absorbable sling or a SIS was used for the index surgery or if they were registered as deceased in GynOp.

The choice of questionnaires for the ten-year follow-up was partly dictated by the questionnaires used in GynOp and partly by the questionnaires used in the LifeGene project; all validated even in their Swedish version (148,152,154,155). LifeGene is a prospective cohort study with longitudinal follow-up, the goal of which is to collect and make available data and samples from 250,000 Swedes (156). LifeGene is planned to be employed for a study that is part of this project

and aims to compare our cohort with a cohort of women not operated upon with a MUS. Eligible women were contacted by letter ten years after the index operation. In November 2020, women were invited to participate in our study answering questionnaires regarding urinary tract-related symptoms (UDI-6), the impact of incontinence on sexual function (PISQ-12) and quality of life parameters (IIQ-7), the impression of improvement along with questions regarding background information and possible mesh-related complications postoperatively. Mesh-related complications that were recorded included urinary retention, vaginal bleeding, vaginal tightness, pelvic pain, dyspareunia, verified tape exposure, tape erosion into the bladder or bowel, inflammation/infection of the tape, fistula, reoperation, partial or total removal of the tape, repeated operation for incontinence and persisting sling-related symptoms at ten years.

Women were asked to assess whether there was a possible relation between their symptoms and the MUS surgery. Persisting symptoms were defined as those still present at the ten-year follow-up. The term "retention" is used for the symptom defined by ICS as the complaint of the inability to empty the bladder completely, both preoperatively and postoperatively. Participating women could answer either by mail, using enclosed envelopes, or electronically, using an online survey platform constructed by us. Women that did not answer the first invitation received a reminder letter after two months. Information about the study was enclosed in the invitation letter, and answering the questionnaires was regarded as consent to participate in the study.

Descriptive and analytical statistics were employed managing and presenting the collected data. Mean, standard deviation and range were used when analyzing continuous data, whereas median, interquartile range and frequencies were used for ordinal and nominal data. Chi-squared test and Fisher's exact test were used for comparison between groups, when nominal data were analyzed, and Mann-Whitney U test was used with ordinal and non-normally distributed data. Binary logistic and linear regression analysis was used to adjust the results of group comparisons for possible confounders and to identify perioperative predictors for SUI, UUI, impression of improvement, urinary retention, pelvic pain, dyspareunia and persistent symptoms due to complications at ten years. The potential predictors that were tested were age, body mass index (BMI), parity, the American Society of Anesthesiologists physical status classification system (ASA-group), diabetes, smoking, type of incontinence, previous incontinence surgery, urinary retention, antibiotic prophylaxis, type of incontinence surgery and complications under the first year postoperatively. Results are presented using adjusted odds ratio (OR) and 95% confidence interval (CI). The significance level was set to 5%. Analyses were performed using IBM SPSS Statistics 28.

Study IV

This is a retrospective study for the assessment of the efficacy and safety of PSG use in POP surgery. The medical records of women operated for POP with the enhancement of PSG during a four-year period (November 2011-October 2015) at the Department of Gynecology and Obstetrics in Odense University Hospital, Denmark were reviewed. Participants were identified by the ICD-10 code corresponding to the procedure and confirmed by their operation reports. We included all women having PSG implanted irrespective of the compartment of interest or concomitant surgery. Data were extracted by the undersigned from the electronic medical records of the department using a standardized protocol created for this study. The procedure was overseen and evaluated by professor Martin Rudnicki.

Clinical data at admission, during hospital stay, at discharge and for at least three years postoperatively were reviewed in all cases. All women were examined for residual urine at admission and at discharge and volumes less than 150 ml were considered satisfactory. PSG was used in cases of recurrence of POP after previous POP surgery or in primary POP surgery when the risk for recurrence following native tissue repair was considered by the surgeon to be high. All women were referred to the Department of Gynecology and Obstetrics in Odense by gynecologists from other establishments in Denmark due to their high-risk nature. In case of recurrence of POP that required surgery after index PSG-enhanced repair, women were either treated locally or were referred to a clinic in Copenhagen when sacrocolpopexy was regarded to be the most suitable option.

The stage of prolapse was assessed according to the POP-Q system and prolapse stage ≥ 2 was defined as significant. Recurrence rates were studied only for compartments where PSG was applied. Surgical complications were graded according to the Clavien-Dindo classification system and complications of grade $\geq$ III were defined as major (157). Complications were registered when recorded by health care professionals as an unfavorable evolution of the surgery or stated as a problem (persistent or resolved) by the patients at a follow-up visit. A distorted vaginal shape at examination due to shrinkage, with or without pain, producing a stricture was recorded as vaginal deformation. Stress or urge urinary incontinence/urgency were recorded when either de novo or exacerbated symptoms were described. Persistent complications were considered those present at three-month follow-up.

The surgical procedures were performed by four gynecologists trained in urogynecology with previous experience in the use of mesh in POP surgery. When applied to the anterior vaginal wall, PSG was sutured bilaterally to the arcus tendineus after anterior colporrhaphy without any other modification to the technique compared to native tissue repair. When applied to the posterior wall, PSG was sutured to the rectovaginal fascia, either following midline plication or in the context of site-specific repair. When applied for the support of the apical

compartment, PSG was sutured to the uterosacral ligaments. Absorbable sutures were used in all cases, either polyglactin or polydioxanone sutures, and all patients were administered antibiotic prophylaxis perioperatively (Cefotaxime 1 gram and Metronidazole 1 gram intravenously).

All women were invited to a three-month follow-up visit. During that visit, women were asked about the presence of possible surgery-related complications and assessment of such complications as well as recurrence of prolapse was made based both on women's symptoms and the results of a physical examination. The evaluation was done by either the operating surgeon or another gynecologist of the department and possible complications were reported without the use of any standardized protocol. The women who did not attend the visit were contacted by telephone and were included in the analysis of the postoperative complications without being included in the analysis of the recurrence of prolapse.

Descriptive and analytical statistics were derived from the collected data. Mean, standard deviation and range were used for continuous data, whereas median, interquartile range and frequencies were used for ordinal and nominal data. Logistic regression analysis was employed to identify independent risk factors for the manifestation of complications as well as the recurrence of prolapse after PSG-augmented repair. Age, BMI, menopausal status, number of childbirths, smoking, estrogen use, diabetes, chronic obstructive pulmonary disease, previous hysterectomy, previous POP surgery, previous POP surgery at the same compartment as the graft application, compartment operated with PSG, concomitant hysterectomy and duration of surgery were tested as potential predictors for the manifestation of complications. The above mentioned variables along with duration of hospital stay and manifestation of complications were tested as potential predictors for recurrence of prolapse after PSG-augmented repair. Complications and recurrence of prolapse were analyzed as binary variables (yes/no). Univariate analysis was performed and the potential predictors that achieved statistical significance < 0.1 were used in a backward stepwise logistic regression analysis with likelihood ratio testing, where statistical significance < 0.05 was required for a predictor to be included in the final model. Goodness-of-fit of the model was assessed using the Hosmer-Lemeshow test ($p > 0.05$) and predictive power was assessed using the Nagelkerke's R^2 measure. Results on adjusted OR and 95% CI are presented. Analyses were performed using IBM SPSS Statistics 26.

Ethical issues

Study I

The ethical issues that rise from this study concern the initial part of the trial with the use of Ajust® but also the three-year follow-up of the operated women. In both cases, the risks associated with the completion of the study were considered to be minor compared to the potential benefit. The use of a new device, not adequately studied, particularly regarding its long-term performance, involves some degree of risk for the women receiving it, mainly with respect to its efficacy. The risk for complications associated with the application of the anchoring mechanism of Ajust® was not considered to be significant as there has been no indication of such a risk in previous SIS studies. On the contrary, Ajust®, and SIS in general, were designed in order to minimize the risk for undesired effects that can derive from the use of slings. At the same time, Ajust® was already commercially available and women received it for the treatment of SUI even outside of the frame of a research setting. This makes the significance of conducting the study larger and the threshold for the acceptance of device-related risks higher. The same applies even more to the three-year follow-up during which the main risks lie in disturbing the women's privacy. The key point for accepting those risks is the informed consent that the participating women provided. Ethics approval of the study was obtained from the local ethics committee in each country; Denmark ref. no. SJ252 (approved by the local ethics committee of Region Zealand, Denmark), Sweden ref. no. 2011/529, 2012/42 (approved by the regional ethics committee in Lund, Sweden), Norway ref. no. 2011/2005A (Ethics committee of Norway, REK). The trial was registered at ClinicalTrials.gov: NCT01754558.

Study II & III

The disturbance of women's privacy is the main ethical issue of this project. Contacting women more than ten years after a surgery for the treatment of SUI might cause negative feelings and frustration both to women themselves but also to their relatives or people taking care of them, as many of the women are expected to be very old at the time the study takes place. Extra care was taken to ensure that the risk for unauthorized access to women's personal information would be as low as possible. This was done through analyses performed in the

remote desktop environment of GynOp, without being able to extract any data, along with the use of pseudonymised databases when information was handled outside of the university or the department data setting. Ethical approval for this study was obtained from the Swedish Ethical Review Authority, dnr 2019-02529. The trial was registered at ClinicalTrials.gov: NCT04558762.

Study IV

Considering the retrospective design of this study, the ethical issues that rise from it relate almost entirely to the safety of the personal information of the participating women. This was secured by using identifiable information only when working with the computers at the department collecting data from the medical records of the women. Any information that left this environment was pseudonymised, while the key matching the pseudonymised information to the women never left this environment. According to Danish legislation, observational non-interventional studies do not require approval from the national ethics committee. The study was approved by the board of Odense University Hospital, ref. no. 18/19689.

Results

Study I

Out of the 305 women that were initially allocated to a treatment group in the eight centers, 279 women were enlisted in the seven centers that participated in the three-year follow-up. Of those 279 women, 259 participated in the one-year follow-up and were contacted three years after the surgery. After three years, 205 women responded answering our questionnaires resulting in a response rate of 73.5%. Figure 7 displays a flowchart of the study population. There was no difference found in baseline characteristics or preoperative bladder function between the two groups, besides residual urine volume that was though very low for both groups (Table 1).

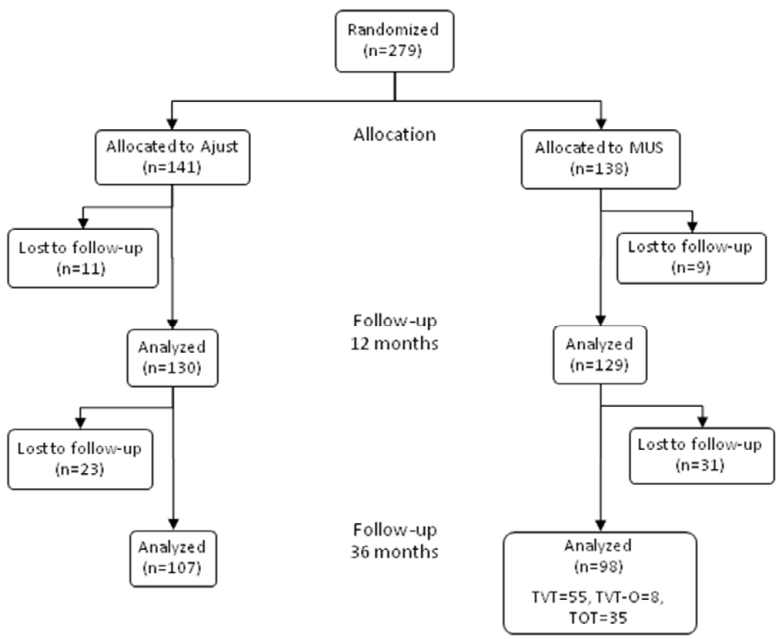

Figure 7. Flowchart of the study population

Table 1. Descriptive characteristics at baseline of the 279 participants.

	Ajust (n=141)	MUS (n=138)	P-value
Age (years), mean ± SD (range)	44.9 ± 6.8 (27-59)	45.9 ± 7.3 (27-60)	0.228 [a]
BMI (kg/m²), mean ± SD (range)	26.2 ± 4.8 (19-49)	26.6 ± 4.6 (16-42)	0.550 [a]
Parity, median (IQR)	2.0 (1.0)	2.0 (1.0)	0.697 [b]
Postmenopausal, n (%)	28 (20.3)	32 (24.4)	0.415 [b]
On HRT, n (%)	15 (10.6)	18 (13.1)	0.519 [b]
- Systemic HRT, n (%)	6 (17.6)	5 (14.7)	0.745 [b]
- Vaginal HRT, n (%)	10 (30.3)	13 (37.1)	0.551 [b]
Smokers, n (%)	25 (18.0)	21 (15.4)	0.572 [b]
Diabetes, n (%)	0 (0.0)	4 (2.9)	0.060 [c]
Chronic Obstructive Lung disease, n (%)	3 (2.2)	2 (1.5)	0.503 [c]
Previous hysterectomy, n (%)	15 (10.7)	15 (10.9)	0.967 [b]
Previous prolapse surgery, n (%)	3 (2.1)	2 (1.4)	0.507 [c]
- Anterior	2 (66.9)	2 (100)	
- Anterior & Posterior	1 (33.3)	0 (0.0)	
Medication, n (%)			
- Diuretics	3 (2.1)	4 (2.9)	0.722 [c]
- Antidepressants	8 (5.8)	6 (4.4)	0.603 [b]
Stress urinary incontinence, n (%)	104 (74.8)	108 (80.6)	0.252 [b]
Mixed urinary incontinence, n (%)	36 (26.1)	29 (21.2)	0.337 [b]
Number of micturitions per day, mean ± SD (range)*	7.2 ± 2.1 (3-15)	7.0 ± 1.7 (3-13)	0.259 [a]
Incontinence episodes per day, mean ± SD (range)*	3.2 ± 3.4 (0-24)	3.3 ± 4.0 (0-26)	0.721 [a]
ICIQ score, median (IQR)	15.0 (5.0)	15.0 (4.0)	0.106 [d]
Residual vol., median (IQR)	5.0 (30.0)	2.5 (19.3)	0.037 [d]
Flow max rate (ml/sec), mean ± SD	27.9 ± 8.5	27.6 ± 12.5	0.897 [a]
Dyspareunia, PISQ-12 (%)			0.505 [d]
- Always	1.6	0.9	
- Usually	2.5	2.6	
- Sometimes	21.3	23.1	
- Seldom	30.3	35.0	
- Never	44.3	38.5	

*Calculated from the bladder diary
[a] Student's t-test, [b] Chi-square test, [c] Fisher's exact test, [d] Mann-Whitney U test

No difference was found between the Ajust® and the MUS group regarding subjective cure rate. This was the case when subjective cure rate was defined as the percentage of women reporting no leakage at all in the ICIQ-UI-SF. The percentage of women that stated being totally continent at three years was 50.9% in the Ajust® and 51.5% in the MUS group. No significant difference was found when the definition of cure was based on the two-day bladder diary, with 71.1% and 82.9% of the women in the Ajust® and the MUS group respectively having no registered incontinence episode (Table 2).

Table 2. Results at 36-months follow-up.

	Ajust (n=107)	MUS (n=98)	P-value
Subjective cure rate, ICIQ-UI-SF (%)			
Question 3: "How often do you leak urine?"			0.909 [a]
- Never	50.9	51.5	
- About once a week or less often	31.1	32.0	
- Two or three times a week	12.3	10.3	
- Once daily	3.8	1.0	
- Several times a day	1.9	5.2	
- All the time	-	-	
ICIQ score sum, question 3-5 (mean ± SD)	2.8 ± 3.6	3.0 ± 3.9	0.660 [b]
Number of micturitions per day (mean ± SD)	6.1 ± 1.4	6.7 ± 1.8	0.040 [b]
Incontinence episodes, bladder diary, n (%)			0.481 [a]
- Zero episodes	27 (71.1)	29 (82.9)	
- One episodes	5 (13.2)	3 (8.6)	
- Two episodes	4 (10.5)	1 (2.9)	
- Three episodes	1 (2.6)	-	
- Four episodes	-	2 (5.8)	
- > four episodes	1 (2.6)	-	
Dyspareunia, PISQ-12 (%)			0.496 [a]
- Always	0.0	1.3	
- Usually	4.5	1.3	
- Sometimes	15.7	10.0	
- Seldom	22.5	41.3	
- Never	57.3	46.3	
PISQ-12 score sum (mean ± SD)	36.1 ± 3.7	35.1 ± 3.7	0.086 [a]

[a] Mann-Whitney U test, [b] Student's t-test

The ICIQ-UI-SF score sum was equally reduced in both groups at three-year follow-up (Table 2) and equal over-the-time improvement was also observed regarding urgency and UUI based on the ICIQ-OAB questions 5a and 6a (Table 3). The two groups demonstrated similar degree of improvement as stated in the PGI-I questionnaire, with the percentage of women reporting significantly or much improved three years after the operation with Ajust® being 95.1% versus 89.7% for the women who received MUS. For both groups the improvement increased through the first postoperative year, remaining stable at the same level during the three-year follow-up. The same pattern was observed using the PGI-S questionnaire with equal degrees of improvement of the severity status after three years between the groups, which was stable compared with the one-year results (Table 4). Similarly, there was no difference observed in the percentage of women reporting dyspareunia after the operation or in the PISQ-12 score sum (Table 2). No major adverse events other than those reported at the 1-year follow-up were later recorded.

Table 3. ICIQ-OAB results of the 205 women analyzed after 36 months.

	Baseline	12 months	36 months	P-value (post hoc)
ICIQ-OAB, Question 5a [Ajust] %				< 0.001 [a]
"Do you have to rush to the toilet to urinate?"				(A, B)
- Never	15.8	31.1	28.3	
- Rarely	33.7	43.7	48.1	
- Sometimes	38.6	19.4	17.9	
- Often	10.9	4.9	4.7	
- Always	1.0	1.0	0.9	
ICIQ-OAB, Question 5a [MUS] %				< 0.001 [a]
"Do you have to rush to the toilet to urinate?"				(A, B)
- Never	14.0	29.9	28.6	
- Rarely	36.6	46.0	37.8	
- Sometimes	44.1	24.1	28.6	
- Often	5.4	-	5.1	
- Always	-	-	-	
ICIQ-OAB, Question 6a [Ajust] %				< 0.001 [a]
"Does urine leak before you can get to the toilet?"				(A, B)
- Never	21.6	50.4	48.1	
- Rarely	27.0	35.0	31.1	
- Sometimes	36.0	12.2	18.9	
- Often	12.6	2.4	1.9	
- Always	2.7	-	-	
ICIQ-OAB, Question 6a [MUS] %				< 0.001 [a]
"Does urine leak before you can get to the toilet?"				(A, B)
- Never	22.4	56.5	50.0	
- Rarely	36.4	33.0	30.2	
- Sometimes	33.6	7.8	15.6	
- Often	5.6	1.7	3.1	
- Always	1.9	0.9	1.0	

[a] Friedman test with Wilcoxon signed-rank test as post-hoc, Bonferroni method → alpha=0.017
Post-hoc test: A=Significant difference between baseline-12 months, B=baseline-36 months, C=12-36 months

Table 4. PGI-S and PGI-I results of the 205 women analyzed after 36 months.

	Ajust baseline	Ajust 12 months	Ajust 36 months	MUS baseline	MUS 12 months	MUS 36 months
PGI-S, % [a]						
- Normal	28	72.3	68.3	31.9	86.4	70.1
- Minor	5.0	25.7	27.9	12.1	13.6	22.7
- Moderate	40.0	2.0	2.9	38.5	-	6.2
- Severe	27.0	-	1.0	17.6	-	1.0
PGI-I, % [b]						
- Very much improved	-	75.0	71.6	-	89.5	75.3
- Much improved	-	19.0	23.5	-	4.7	14.4
- Minimally improved	-	4.0	3.9	-	3.5	7.2
- Unchanged	-	2.0	-	-	1.2	2.1
- Minimally worse	-	-	-	-	-	-
- Much worse	-	-	-	-	-	1.0
- Very much worse	-	-	1.0	-	1.2	-
Ajust: n=107, MUS: n=98						

[a] Comparison of PGI-S between Ajust and MUS at baseline; **p=0.033**, 12 months; p=0.115 and 36 months; p=0.913 (Mann-Whitney U-test)
[b] Comparison of PGI-I between Ajust and MUS at 12 months; **p=0.028** and 36 months; p=0.759 (Mann-Whitney U-test)

Study II & III

Out of 4894 women that were identified through GynOp to have received a MUS, 4348 were sent an invitation to participate and 2555 responded (response rate 58.8%). Examination of the participants' operative reports from GynOp showed that nine women received an absorbable sling and 125 women a single-incision sling and were therefore excluded (Figure 8). The remaining 2421 women that responded and were included in the analyses had a mean age of 64 years and a mean follow-up time of 10.9 years (range 9-14 years). Responders were at baseline significantly younger, had lower BMI, smoked less, had lower ASA-score and lower incidence of diabetes, previous incontinence surgery and MUI than non-responders. Baseline data of the participating women are presented in Table 5. A RP sling was used in 1562 women and TO in 859 women. Women operated with TO sling had at baseline significantly higher BMI, lower ASA-group and had diabetes, previous incontinence surgery and were smokers at higher degree compared to women operated with RP. Most women had pure SUI, according to the physicians' report. Data obtained through GynOp are presented in Table 6.

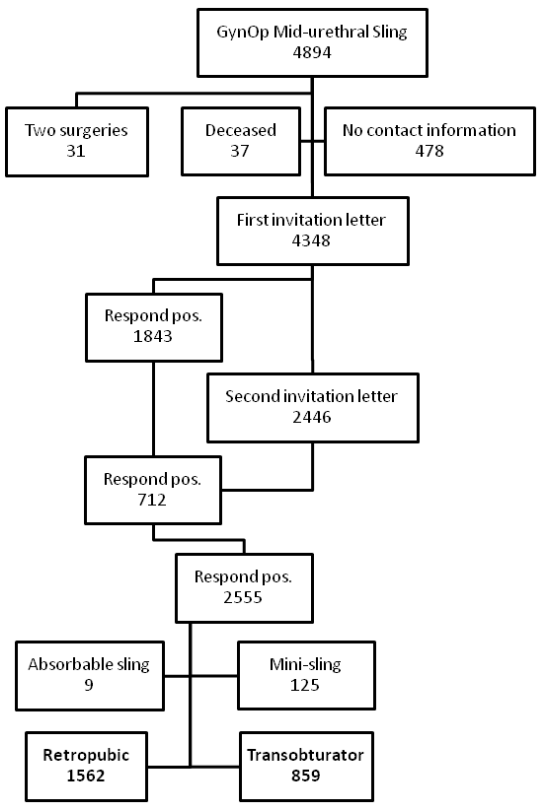

Figure 8. Flowchart of the study population

At the ten-year follow-up, SUI was reported by 36.7% of the participants. Of all women having received a MUS, 91.6% reported being better or much better after one year and 79.2% after ten years compared to their preoperative condition. At the ten-year follow-up, SUI, urgency and UUI were significantly more common among women having received a TO sling compared to the RP group. Women in the RP group also reported significantly lower UDI-6 scores and higher levels of improvement at ten years (RP 80.8% vs. TO 76.3%, p=0.004) even though there was no significant difference between the two groups at the 1-year follow-up (RP 92.2% vs. TO 90.6%, p=0.2). Pelvic pain was reported by 17.5% of the participating women and dyspareunia by 15.8% with no difference between the two groups. No difference was detected between RP and TO groups regarding PISQ-12 or IIQ-7 scores at ten years (Table 7).

Sling-related symptoms at any time during the ten years postoperatively were reported by 24.8% of the women, while 17.7% reported persisting symptoms at the ten-year follow-up, with no difference between the RP and TO technique. The most common symptom regarded to be sling-related by the participants was urinary retention (11.2%) and the second most common was dyspareunia (5.5%). No difference was recorded between women operated with RP or TO sling regarding sling-related pelvic pain, dyspareunia, specific sling-related complications or reoperations due to complications. The percentage of women reporting sling-related pelvic pain was 3.7%, sling-related dyspareunia 5.5% and mesh exposure 2.0%. Repeated surgery for incontinence after the first sling procedure was reported by 6.9% of the participating women, significantly more in the TO group (9.1% vs. 5.6% in RP group) (Table 8). The same findings were recorded when analyses comparing RP and TO groups were adjusted for age, BMI, parity, diabetes, smoking, ASA-group, type of incontinence and previous incontinence surgery using binary logistic or linear regression analysis, except for improvement at ten years and UUI, where the difference between the two groups was not proven to be significant after adjusting for potential confounders.

Table 5. Baseline characteristics

	n=2421	Retropubic n=1562	Transobturator n=859
Age (years), mean ± SD (range)	53.2 ± 11.0 (23-85)	52.9 ± 11.1 (23-85)	53.6 ± 10.7 (23-83)
BMI, median (IQR)	25.4 (5.5)	25.2 (5.4)	25.8 (5.3)
Parity, median (IQR)	2 (1)	2 (1)	2 (1)
Smoking status, n (%)			
- Yes	235 (11.6)	149 (11.3)	86 (12.3)
- No	1785 (88.4)	1174 (88.7)	611 (87.7)
ASA-class, n (%)			
- 1/2	2339 (98.6)	1512 (98.6)	827 (98.6)
- 3/4	34 (1.4)	22 (1.4)	12 (1.4)
Previous incontinence surgery, n (%)			
- Yes	116 (4.9)	69 (4.5)	47 (5.6)
- No	2247 (95.1)	1460 (95.5)	787 (94.4)
Diabetes, n (%)			
- Yes	70 (3.6)	39 (3.0)	31 (4.7)
- No	1884 (96.4)	1252 (97.0)	632 (95.3)
Type of incontinence, n (%)			
- SUI	1806 (76.4)	1186 (77.5)	620 (74.3)
- MUI	532 (22.5)	327 (21.4)	205 (24.6)
- UUI	11 (0.5)	7 (0.5)	4 (0.5)
- Other	5 (0.2)	4 (0.3)	1 (0.1)
- No incontinence	11 (0.5)	7 (0.5)	4 (0.5)

Multivariable binary logistic regression analysis revealed that type of incontinence other than pure SUI, previous incontinence surgery and preoperative urinary retention were predictors for SUI, UUI and lack of improvement at ten-year follow-up. Preoperative urinary retention and complications during the first year after the surgery were predictors for persisting symptoms due to complications at ten years. Older age was a predictor for UUI and lack of improvement at ten years, while younger age was a predictor for urinary retention and pelvic pain. Higher BMI, diabetes and complications during the first postoperative year were also found to be significant predictors for lack of improvement at ten years. Looking separately at the two surgical techniques, we found that MUI and preoperative retention were predictors for lack of improvement only in the RP group, whereas higher BMI, diabetes and previous incontinence surgery were predictors for lack of improvement only in the TO group. No outcome was found to be associated with weight gain during the ten postoperative years.

Table 6. Perioperative data

	n (%) n=2421	Retropubic	Transobturator
Perioperative cystoscopy			
- Yes	1543 (63.7)	1527 (97.8)	16 (1.9)
- No	878 (36.3)	35 (2.2)	843 (98.1)
Bladder perforation	52 (2.1)	50 (3.2)	2 (0.2)
Antibiotic prophylaxis			
- Yes	2019 (83.5)	1415 (90.8)	604 (70.3)
- No	399 (16.5)	144 (9.2)	255 (29.7)
Perioperative complication			
- No	2334 (96.4)	1498 (95.9)	836 (97.3)
- Mild	85 (3.5)	63 (4.0)	22 (2.6)
- Severe	2 (0.1)	1 (0.1)	1 (0.1)
Bleeding	23 (1.0)	15 (1.0)	8 (0.9)
Bladder injury	47 (1.9)	45 (2.9)	2 (0.2)
Urethra injury	2 (0.1)	1 (0.1)	1 (0.1)
Complication during hospital stay			
- No	2216 (94.0)	1444 (93.9)	772 (94.0)
- Mild	136 (5.8)	89 (5.8)	47 (5.7)
- Severe	5 (0.2)	4 (0.3)	1 (0.1)
- Complication of unknown grade	1 (0.0)	0 (0.0)	1 (0.1)
Urinary retention	34 (1.4)	18 (1.2)	16 (1.9)
Infection	6 (0.3)	3 (0.2)	3 (0.4)
Pain	22 (0.9)	10 (0.6)	12 (1.5)
Reoperation during hospital stay	20 (0.8)	17 (1.1)	3 (0.3)
Complication existing at 2 months			
- No	1994 (86.6)	1307 (87.3)	687 (85.3)
- Mild	285 (12.4)	174 (11.6)	111 (13.8)
- Severe	23 (1.0)	16 (1.1)	7 (0.9)
Urinary retention	65 (2.8)	38 (2.5)	27 (3.3)
Pain	133 (5.7)	81 (5.3)	52 (6.4)
Infection	160 (7.6)	105 (7.5)	55 (7.7)
Complication existing at 1 year			
- No	2075 (94.3)	1363 (95.0)	712 (93.0)
- Mild	112 (5.1)	64 (4.5)	48 (6.3)
- Severe	14 (0.6)	8 (0.6)	6 (0.8)
All complications during first year postoperatively			
- No			
- Mild	1811 (80.4)	1197 (81.0)	614 (79.1)
- Severe	417 (18.5)	262 (17.7)	155 (20.0)
	25 (1.1)	18 (1.2)	7 (0.9)
Any reoperation 1 year			
- Yes	35 (1.7)	23 (1.7)	12 (1.7)
- No	2037 (98.3)	1354 (98.3)	683 (98.3)

Table 7. Bladder and pevic function at 10 years

	n (%)	Retropubic	Transobturator	P
Stress urinary incontinence				**<0.001***
- Yes	871 (36.7)	513 (33.4)	358 (42.8)	
- No	1501 (63.3)	1022 (66.6)	479 (57.2)	
Urgency				**0.001***
- Yes	1139 (47.6)	697 (45.1)	442 (52.1)	
- No	1254 (52.4)	847 (54.9)	407 (47.9)	
Urgency urinary incontinence				**0.004***
- Yes	1376 (57.8)	854 (55.6)	522 (61.7)	
- No	1005 (42.2)	681 (44.4)	324 (38.3)	
Small amounts of leakage				**<0.001***
- Yes	1216 (51.8)	742 (49.1)	474 (56.6)	
- No	1133 (48.2)	770 (50.9)	363 (43.4)	
Urinary retention				0.881*
- Yes	712 (29.7)	458 (29.6)	254 (29.9)	
- No	1683 (70.3)	1088 (70.4)	595 (70.1)	
Improvement				**0.004****
- Much better	1306 (55.2)	876 (57.3)	430 (51.4)	
- Better	567 (24.0)	358 (23.4)	209 (25.0)	
- No change	247 (10.4)	143 (9.4)	104 (12.4)	
- Worse	133 (5.6)	81 (5.3)	52 (6.2)	
- Much worse	112 (4.7)	70 (4.6)	42 (5.0)	
UDI-6 score, median (IQR)	20.0 (38.9)	16.7 (38.9)	22.2 (44.4)	**<0.001****
PISQ-12 score, median (IQR)	36.0 (9.0)	36.0 (9.0)	35.0 (10.0)	0.532**
IIQ-7 score, median (IQR)	19.0 (42.9)	19.0 (42.9)	23.8 (47.6)	0.135**

* Chi-squared test, ** Mann-Whitney U test

Table 8. Questions at 10 years regarding sling procedure

	n (%)	Retropubic	Transobturator	P
Symptoms because of the tape				
- No	1749 (75.2)	1142 (75.7)	607 (74.1)	0.389*
- Bleeding or discharges	23 (1.0)	15 (1.0)	8 (1.0)	0.970*
- Feeling of tight vagina	60 (2.6)	35 (2.3)	25 (3.1)	0.283*
- Urinary retention	261 (11.2)	166 (11.0)	95 (11.6)	0.648*
- Pelvic pain	86 (3.7)	53 (3.5)	33 (4.0)	0.522*
- Dyspareunia	127 (5.5)	78 (5.2)	49 (6.0)	0.399*
Have you had verified				
- Tape exposure	44 (2.0)	32 (2.2)	12 (1.5)	0.287*
- Tape erosion in the bladder	10 (0.4)	7 (0.5)	3 (0.4)	0.518**
- Tape erosion in the rectum	2 (0.1)	2 (0.1)	0 (0.0)	0.424**
- Inflammation/infection of the tape	9 (0.4)	8 (0.5)	1 (0.1)	0.123**
- Fistula	3 (0.1)	1 (0.1)	2 (0.3)	0.279**
- Other	46 (2.1)	24 (1.6)	22 (2.8)	0.062*
- No	2122 (94.9)	1383 (94.9)	739 (94.9)	0.954*
Reoperation because of the tape				0.245*
- Yes	131 (5.6)	79 (5.2)	52 (6.3)	
- No	2221 (94.4)	1450 (94.8)	771 (93.7)	
Parts of the tape removed				0.655*
- Yes	38 (1.7)	26 (1.8)	12 (1.5)	
- No	2196 (98.3)	1426 (98.2)	770 (98.5)	
Whole tape removed				0.777*
- Yes	22 (1.0)	15 (1.0)	7 (0.9)	
- No	2181 (99.0)	1424 (99.0)	757 (99.1)	
Persisting symptoms presently				**0.015***
- Yes	281 (17.7)	162 (15.9)	119 (20.8)	
- No	1309 (82.3)	855 (84.1)	454 (79.2)	
Repeated operation for incontinence after first sling procedure				**0.002***
- Yes	159 (6.9)	85 (5.6)	74 (9.1)	
- No	2160 (93.1)	1420 (94.4)	740 (90.9)	

* Chi-squared test, ** Fisher's exact test

Table 9. Baseline characteristics

n=155	
Age (years), mean ± SD (range)	64.1 ± 10.4 (35-84)
BMI, mean ± SD (range)	26.4 ± 4.4 (18.3-41.4)
Parity, median (IQR)	2 (1)
Postmenopausal, n (%)	116 (74.8)
Estrogen use, n (%)	83 (53.5)
- Vaginal	71 (45.8)
- Systemic	9 (5.8)
- Both	3 (1.9)
- Not known	20 (12.9)
Smoking status, n (%)	
- Smoking	14 (9.0)
- Non smoking	72 (46.5)
- Not known	69 (44.5)
Diabetes, n (%)	16 (10.3)
Chronic obstructive lung disease, n (%)	1 (0.6)
Medication, n (%)	
- Diuretics	48 (31.0)
- Antidepressants	16 (10.3)
- ASA	29 (18.7)
- Warfarin	3 (1.9)
Previous hysterectomy, n (%)	72 (46.5)
Previous prolapse surgery, n (%)	121 (78.1)
- Anterior	108 (69.7)
- Posterior	41 (26.5)
- Apical	43 (27.7)
POP-Q stage ≥ 2, n (%)	
- Anterior	114 (73.5)
- Posterior	72 (46.5)
- Apical	36 (23.2)

SD: standard deviation, IQR: interquartile range, BMI: body mass index, ASA: acetylsalicylic acid, POP-Q: pelvic organ prolapse quantification system

Study IV

In total, 155 women undergoing POP surgery with the use of PSG were identified. Among all women, 121 (78.1%) had previous POP surgery. Six women (3.9%) had previous implantation of PSG but not at the same compartment as the one operated with PSG during the present study. No patients had been operated with any other type of mesh or graft and no concurrent incontinence surgery was performed in any case. The preoperative evaluation of prolapse stage in the different compartments along with the rest of the women's baseline characteristics are presented in Table 9. In 134 cases (86.5%) PSG was applied in one compartment, in 20 cases (12.9%) in two compartments and in one case (0.6%) PSG was applied in all three compartments. The perioperative data in relation to PSG placement along with the proportion of each compartment previously operated for POP are presented in Table 10.

Table 10. Perioperative data

n=155	
Duration of surgery (min), mean ± SD (range)	97.9 ± 34.4 (33-254)
Stay at hospital (hours), n (%)	
- 0-8	5 (3.2)
- 9-12	21 (13.5)
- 13-24	49 (31.6)
- 25-48	62 (40.0)
- >48	18 (11.6)
Compartments operated with PSG during an operation, n (%)	
- Anterior	76 (49.0)
- Posterior	51 (32.9)
- Apical	7 (4.5)
- Anterior + posterior	15 (9.7)
- Anterior + apical	1 (0.6)
- Posterior + apical	4 (2.6)
- Anterior + posterior + apical	1 (0.6)
Compartments operated with PSG in total, n (%)	
- Anterior	93 (60.0)
- Posterior	71 (45.8)
- Apical	13 (8.4)
Women with previous POP surgery at same compartment as current PSG application, n (%)	99 (63.9)
PSG-augmented compartments with previous POP surgery, n (%)	
- Anterior	80 (86.0)
- Posterior	19 (26.8)
- Apical	2 (15.4)

SD: standard deviation, PSG: porcine small intestinal submucosa graft, POP: pelvic organ prolapse

Of the 155 women included in our study, 138 (89.0%) attended the three-month follow-up physical examination. Twelve of the 17 women that did not attend were contacted by telephone and were included in the analysis of complications. At three-month follow-up, 22 women (15.9%) demonstrated POP-Q stage ≥ 2 in a compartment operated with PSG. The anatomical recurrence rates for each compartment supported with PSG are shown in Table 11. Assessment of the hospital records during the following three years revealed that 13 out of 155 women (8.4%) underwent reoperation because of prolapse at the compartment where PSG was applied, along with seven additional women that expressed prolapse-related symptoms postoperatively with no records of reoperation.

Table 11. Data at 3-month follow-up

n=138	
Women with recurrence in PSG-augmented compartment at 3 months, n (%)	
- No	116 (84.1)
- Yes	16 (11.6)
- Recurrence in one of two compartments	6 (4.3)
PSG-augmented compartments with recurrence at 3 months, n (%)	
- Anterior	19 (22.6)
- Posterior	3 (4.8)
- Apical	0
n=150	
Women with any complication during first 3 months, n (%)	84 (56.0)
According to compartment:	
- After anterior PSG application	46 (50.0)
- After posterior PSG application	46 (69.7)
- After apical PSG application	10 (76.9)
Women with major complications during first 3 months, n (%)	8 (5.3)
According to compartment:	
- After anterior PSG application	2
- After posterior PSG application	3
- After apical PSG application	1
- After anterior + posterior PSG application	1
- After posterior + apical PSG application	1
Women with persistent complications at 3 months, n (%)	42 (28.0)
According to compartment:	
- After anterior PSG application	16 (17.4)
- After posterior PSG application	26 (39.4)
- After apical PSG application	4 (30.8)

PSG: porcine small intestinal submucosa graft

Complications registered perioperatively and under a three-month period postoperatively disclosed 84/150 women (56%) experiencing at least one complication. The most common complications were urinary retention in 28 cases (18.7%) and pain in 18 cases (12.0%). Major complications (all third grade) were observed in eight cases (5.3%). In all cases reoperation was performed within three months after the index operation; in four cases for the removal of sutures causing urinary retention, in two cases because of graft exposure, in one case because of painful vaginal septum at the site of PSG implantation (shrinkage) and in one case for the removal of sutures causing ureteral obstruction. Persistent complications at three months were reported in 42/150 cases (28%). The most common complications reported at three months were vaginal deformations, dyspareunia, SUI, UUI and pain. The distribution of complications (any, major and persistent) to each compartment is presented in Table 11 and the detailed list of complications is presented in Table 12. The long-term evaluation of the women's medical records revealed no additional contacts with the treating hospital for complications other than those already recorded.

Table 12. List of complications

Incidence of complications during first 3 months, n (%)			
- Urinary retention	28 (18.7)	- Wound infection	8 (5.3)
- Pain	18 (12.0)	- Mesh exposure	6 (4.0)
- Urinary tract infection	13 (8.7)	- Granulation tissue/bleedings	5 (3.3)
- Blood loss perioper. > 200 cc	11 (7.3)	- Shortened vagina	4 (2.7)
- Vaginal deformation	10 (6.7)	- Needle/part of needle left at oper. site	2 (1.3)
- Hematoma	10 (6.7)	- Bladder perforation	1 (0.7)
- Dyspareunia	9 (6.0)	- Ureteral obstruction	1 (0.7)
- Stress urinary incontinence	9 (6.0)	- Pain at urination	1 (0.7)
- Urgency/urge urinary incontinence	8 (5.3)	- Defecation problems	1 (0.7)
Persistent complications at 3 months, n (%)			
- Vaginal deformation	10 (6.7)	- Shortened vagina	4 (2.7)
- Dyspareunia	9 (6.0)	- Urinary tract infection	2 (1.3)
- Stress urinary incontinence	9 (6.0)	- Needle/part of needle left at oper. site	2 (1.3)
- Urgency/urge urinary incontinence	8 (5.3)	- Urinary retention	1 (0.7)
- Pain	6 (4.0)	- Pain at urination	1 (0.7)
- Granulation tissue/bleedings	5 (3.3)	- Defecation problems	1 (0.7)

The logistic regression model for recurrence following PSG repair demonstrated a significant effect only for previous prolapse surgery at the same compartment as the PSG application. Significant predictors for the manifestation of complications were women's lower age, smoking and longer duration of surgery (Table 13). Among the different types of complications, lower age was associated with pain and longer duration of surgery was associated with vaginal deformations, blood loss and needle/part of needle left at operation site, as demonstrated through univariable logistic regression analysis. Smoking was not significantly associated with any particular complication.

Table 13. Logistic regression analysis for significant predictors (final models).

	Coefficient	**Significance**	**Exponentiated coefficient**	**95% CI for exp. coefficient**
Recurrence in compartment with PSG application				
Previous prolapse surgery at the same compartment	1.426	0.028	4.162	1.165-14.868
Constant	-2.730	0.000	0.065	
Complication during first 3 months				
Age	-0.041	0.034	0.960	0.924-0.997
Smoking status (reference group non smoking)		0.022		
- Smoking	1.421	0.058	4.140	0.952-17.996
- Not known	0.952	0.016	2.590	1.194-5.617
Duration of surgery	0.019	0.003	1.019	1.007-1.031
Constant	0.618	0.666	1.855	

PSG: porcine small intestinal submucosa graft, CI: confidence interval

Discussion

Study I

Based on the results of the study comparing Ajust® with conventional MUS, Ajust® demonstrates equal efficacy and safety to the widely used mid-urethral slings, whose characteristics have been confirmed by years of clinical experience and long-term follow-up trials. Furthermore, both methods seem to have a positive effect on overactive bladder symptoms. This has been shown in other studies evaluating the effect of surgical treatment for MUI and it has been used as an argument by those supporting a common urethrogenic mechanism as the cause of both SUI and UUI (15). Compared with the 1-year results from the study of Rudnicki et al. (146), the 3-year outcomes do not differ substantially regarding the cure rates, the overactive bladder symptoms, the perception of improvement or the dyspareunia for either Ajust® or MUS. This is confirmed by the analysis of the outcomes in our group of women over time, suggesting an invariable efficacy and safety of Ajust® after the first year and up to 3 years. The same was observed through long-term follow-up studies of other adjustable SIS that demonstrated only a minimal decrease in their effect over the years (105,122,158).

The strength of this study lies in the large number of women recruited, in addition to the multicenter, randomized design, which allows the comparison of Ajust® to other established MUS. In addition, not just one sling was used in the control group of the study, but each center used the type of sling they preferred, making it easier to generalize the conclusions. Meta-analyses have in fact shown that all three MUS used in this study demonstrate similar efficacy (67,69,75). Moreover, Ajust® was not proven to be inferior to conventional MUS, despite the fact that surgeons were not equally familiar with the Ajust® procedure.

There are some limitations regarding this study. The results are patient-reported and they are limited to three years after the operation. Objective data could not be obtained owing to a lack of alignment among the centers participating in the study. Sensitivity analysis was not done as we did not observe any tendency for any of the groups to consistently overcome the others and there were no signs of non-significant p values due to the sample size. Selection bias may occur, but the number of women missing at the three-year follow-up is balanced between the two groups. In fact, the women who did not respond to our invitations were of younger age in both groups. One explanation may be that a large number of non-responders were satisfied with the operation and that, to some extent, we may have

underestimated the cure rates in both groups. We have no reason to believe that the one missing center in particular would affect the outcomes of the study, based on the one-year results. The women included in this study were under 60 years of age and the conclusions do not apply beyond this age group.

This study is one of only two evaluating the performance of Ajust® separately and one of few evaluating the performance of adjustable mini-slings as a group for periods longer than two years (107,158–160). Therefore, the comparison of our results with those of other studies presents significant difficulties. Kluz et al. (159) reported in a retrospective design on the outcomes of Ajust® 36-50 months after the operation. The post-operative evaluation was carried out through a combination of interview and examination and the observed cure rate of 51.6% is in agreement with our results based on the ICIQ-UI-SF. However, the cure rates reported by the remaining studies evaluating the efficacy of Ajust® up to two years are significantly higher at around 85% (118–131). On the other hand, the cure rate we observed of 71.1-82.9% based on the bladder diary was comparable with these studies and the same was observed for the percentage of women reporting to be significantly/much better, which was up to 95.1%. This discrepancy can be explained by the more objective character of the bladder diary in addition to its shorter period of registration, probably resulting in higher specificity, whereas the ICIQ provides a more comprehensive impression of the women's symptoms, which in turn may generate greater sensitivity for detecting incontinence and, therefore, lower cure rates. After all, the correlation between data derived from bladder diaries and questionnaires regarding urinary incontinence is generally known to be weak (161). However, it is to be noted that the bladder diary was submitted by significantly fewer women than those who answered the questionnaires.

In addition to the different ways in which cure is defined by each study group, variation in follow-up periods and study populations may also contribute to the different outcomes. The inclusion of women with MUI in our study certainly lowers the percentage of those reporting no leakage at all after the procedure, which was our primary outcome. In any case, the randomized design allows us to compare Ajust® with other slings with an established effect on incontinence, showing no significant difference, which is in agreement with the results of the other studies comparing Ajust® with TVT-O (121,123–125,127,129–131). Our findings are also in accordance with the results of meta-analyses regarding patient-reported cure rates for both short- and long-term follow-up periods, when comparing conventional MUS with SIS all together and with Ajust® separately (112), likewise when comparing MUS with the group of adjustable SIS (113).

Ajust®, along with other mesh devices, has been withdrawn from the market. The manufacturing company declares only business reasons for this removal and no safety concerns whatsoever, asking at the same time for the immediate removal even of the unused devices. It remains to be seen if the results of long-term follow-up trials could have an impact on this decision.

Study II & III

The findings of these studies show that MUS perform adequately ten years after the application in a population with both SUI and MUI, with a subjective cure rate of 63.3% and an improvement rate of almost 80%. The high improvement rate suggests a tolerable complications profile, which is supported by the low rate of serious complications reported by the women at ten years. Still, 17.7% of the women report having persisting symptoms because of a sling-related complication ten years after the surgery. It might be false to attribute all the reported symptoms to MUS, but it would be difficult to fully detect the source of the symptoms even with a more objective methodology.

The RP approach seems to perform better than the TO approach, with a gradually increasing difference through time between the two techniques, as suggested by the difference in improvement after one respectively after ten years. The superiority of the RP technique is substantiated not only through the better results regarding SUI but also through the UUI, urgency, UDI-6, the perception of improvement and the reoperation rates for incontinence, most of them also after adjusting for possible confounders. The impact of that difference on quality of life parameters (IIQ-7) was not proven to be significant. It is hard to tell if small changes in incontinence-related outcomes can significantly affect the women's quality of life and to which extent (162).

There are few studies examining potential differences between the RP and the TO techniques with regard to pelvic pain, dyspareunia and sexual function. Some studies have shown higher short-term rates of groin pain and dyspareunia after the insertion of a TO sling (163–174), while the presence of vaginal narrowing and palpable bands under the paraurethral folds seen after the application of a TO sling has been associated with higher rates of de novo dyspareunia (175,176). On the other hand, the insertion of a RP sling can affect the blood flow of the clitoris and is thought to have a higher risk of damage of the dorsal nerve of the clitoris (177,178). However, in spite of the large sample size, no difference was detected between the RP and the TO approach considering sexual function, dyspareunia or pelvic pain. Moreover, no significant differences were seen regarding complications or reoperations due to complications. It is worth considering whether the higher risk for perioperative complications with a RP procedure that several studies report (69) and is even seen in our material from GynOp, is something that truly affects women in the long run.

The subjective design for the follow-up stage in this study is a weakness, as the results are only based upon the interpretation of the questions by the participating women. This is particularly important when assessing the estimated incidence of sling-related complications and reoperations. One of the main challenges of carrying out a large register-based cohort study is to secure the quality of the information provided. Reviewing the participants' medical records at a national level is not possible and the use of diagnostic codes to find sling-related

complications and reoperations is often unreliable (179). At the same time, the biggest strength of this study is the large number of participants, essential to detect rare incidents and compare different techniques, while the prospective enrollment of women in the register minimizes the risk for selection bias. The response rate of almost 60% was satisfying, considering the ten-year follow-up design of the study and the large coverage of GynOp among the Swedish population.

This study was designed and performed aiming to present a relevant picture of the Swedish experience with MUS. The positive results concerning the performance of MUS might be overrepresented, considering the characteristics of the responders when compared to the total of the women contacted. There was, though, no difference in drop-out rates between the two surgical techniques used (response rate: RP 59.5% vs. TO 58.0%, p=0.4). It was not possible to obtain information regarding any concomitant prolapse or other surgery, but in Sweden it is common practice to perform MUS placement as a single procedure. The proportion of women having undergone urodynamic evaluation before the sling surgery is unknown but the value of such an evaluation has not been substantiated in previous studies (180).

Our findings are in line with previous studies extending their follow-up period over 10 years (71,72,132,181–183). In these studies, the subjective cure rate presents some significant heterogeneity (57-89%), but the impression of improvement is consistently around 80%, similarly to our results. The superiority of RP slings in long-term settings compared to TO has been previously demonstrated (132–136) and has been reported even in reviews and meta-analyses (67,75). In our study, both the frequency of repeated incontinence surgery and revision surgery are higher than in previous register-based studies (134,136,182, 184–187). However, the way repeated surgeries are recorded in such studies (mostly using diagnostic codes) can explain this disparity. Our findings regarding tape erosion concur with previous reports that show rates around 2% after ten years (71,183–185). The incidence of retention varies among studies, depending on how retention is defined. When the symptom of incomplete bladder emptying is described, the incidence is, similarly to our study, quite high (182). Accordingly, the prevalence of pelvic pain and dyspareunia ranges from 4.0% to 43.4% and from 1.3% to 45.7% respectively (188), posing great difficulties in making comparisons.

Older age, higher BMI, MUI and previous incontinence surgery were found to be predictors for lack of improvement, which is in agreement with previous studies (189–191). Younger age at surgery was associated with retention, which can partly be attributed to the higher risk for postoperative pain in younger women (192). Based on the results from logistic regression analysis, women with higher BMI, diabetes or previous incontinence surgery might benefit more from receiving a RP sling. On the other hand, women with MUI or preoperative retention might benefit from receiving a TO sling, which might be related to the higher risk for retention after a RP sling procedure, demonstrated in several studies (67,69), as well as the

better results of RP sling after repeated MUS surgery, particularly in women with low urethral pressure (193,194). Houwert et al. reached the same conclusion concerning MUI and previous incontinence surgery for the two different techniques used (195). Women reporting lack of improvement at ten-year follow-up demonstrated a more than doubled risk of suffering from pelvic pain at ten years and an almost three times higher risk of suffering from dyspareunia compared to women reporting improvement. It is difficult to estimate the effect of those symptoms on impression of improvement but they might play an important role. On the other hand, dissatisfaction with the efficacy of a procedure might negatively influence the way other aspects are perceived or conveyed through questionnaires.

The symptom of urinary retention seems to hold a key role not only preoperatively, with its predictive value for the efficacy and the safety of MUS, but also for being the most common sling-related complication reported ten years after the surgery. The high manifestation of retention among postoperative complications has been previously shown (196). However, the significance of obstruction for the performance of MUS has even been occasionally indicated as a working mechanism for the accomplishment of continence (77,197), which is supported by the higher efficacy of RP slings in women with low urethral pressure (193,194). This raises questions regarding the effect of a potentially or deliberately obstructing mechanism on an already -even partially- obstructed system, the cost that must be paid to achieve continence, and the precautions needed to obtain desirable results. The importance of preoperative evaluation of subjective voiding difficulties is also greatly unexplored. Inquiring about such symptoms could show to be as useful as measuring residual urinary volume or even performing urodynamic evaluation in search for signs of obstruction or detrusor underactivity. Moreover, the employment of physiotherapy preoperatively for the management of retention might offer advantages regarding the risk for retention postoperatively. There is though still much that remains unknown considering bladder outlet obstruction in women and major controversies exist regarding its definition, its prevalence and its management (198).

One striking finding in this study is the relatively high percentage of the responders (12.7%) reporting not being aware of having received a sling. It seems that even after 2005 and in a Nordic country, information regarding a sling-procedure for treating urinary incontinence was not adequately perceived by many women.

Study IV

The efficacy of POP surgery with the use of PSG that we recorded is comparable to the efficacy following native tissue repairs, although the variation in reported recurrence rates without the use of implants is significant (199). The same conclusion can be drawn by comparing the site-specific reoperation rate that we

recorded (8.4%) with that of previous studies following native tissue repair, which ranges from 3.4% to 9.7% (17). Additionally, the subjective failure rate of 12.9% in our study is similar to rates of 10.6%-15.0% previously recorded following non augmented prolapse surgery (200). This is in agreement with the findings of randomized trials, demonstrating no benefits of PSG use in POP surgery (141–143).

The recurrence rates after PSG-augmented prolapse repair reported by Armitage et al. and Mouritsen et al. are comparable to ours and, similarly to our findings, Mouritsen et al. identified a previous operation at the same compartment as the only risk factor for recurrence of prolapse (144,145). Sung et al. recorded higher recurrence rate in the posterior compartment (11.9%) (142), while Feldner et al. recorded a 13.8% recurrence rate following PSG-augmented repair of the anterior compartment, though with fewer women having undergone previous POP surgery (139). The proportion of women in our study that did not attend the three-month follow-up (11%) may have affected our results but this is difficult to evaluate as these women do not present any distinctive characteristics.

The high incidence of complications compared to most previous studies (201–204) can partly be attributed to our wide definition of a complication. However, when using a more comparable outcome, such as the incidence of complications of grade ≥ III, our finding of a 5.3% rate is in agreement with previously published incidence rates (201,203–205). Most of these studies report rates that are slightly lower following native tissue repair and a little higher following mesh-augmented repair. Women lost to follow-up (3.2%) may also contribute to a higher incidence of complications.

Exposure and pain/dyspareunia are the most reported complications following PFRS with the use of implant, as they are directly associated with the presence of mesh/graft in the pelvic floor (206). In our study, exposure was observed in six cases (4%). Two of the women underwent revision and, in the remaining four cases, the exposure healed spontaneously with no exposure observed at the three-month follow-up. Meta-analyses reporting on exposure rates of vaginal implants in POP surgery show rates of 4%-11.4% following mesh augmented repair and 0-10.1% following the use of graft (83,199,200,207,208).

Pain appears to be a central theme for women with mesh related complications (209). Pain is the second most common complication we recorded (12%) and adding cases with dyspareunia makes it the most common complication women experienced at the three-month follow-up. The incidence of pain and dyspareunia varies widely among studies (199,208) as the classification recommended by IUGA/ICS is not yet routinely used and is difficult to apply to retrospective studies such as ours. The most commonly reported complication at the three-month follow-up of our study was vaginal deformation (6.7%), a condition referred to in some studies as contraction. Shrinkage has been reported after the use of vaginal meshes and Caquant et al. found an incidence of 11.7% (210). However, data on the risk of shrinkage and deformation after the use of grafts are lacking. Vaginal deformation can also be regarded as a pain-related condition, as pain/dyspareunia

is most often associated with this complication. In our study there was, accordingly, a strong link between vaginal deformations and pain with almost half of the women with pain/dyspareunia at three month follow-up, presenting with vaginal deformation (7 out of 15).

Urinary tract-related complications were also extensively represented in our results with urinary retention being the complication with the highest incidence (18.7%). In most cases retention was resolved spontaneously within a few days after the surgery but reoperation was needed in four cases and retention persisted after three months in one case. De novo or exacerbated SUI and UUI were frequently observed without any decline during the postoperative period. This is in agreement with previous observations but there is great discrepancy regarding the definition of this group of complications (199). In our study urinary incontinence was assessed based on women's subjective reports at the three month follow-up visit.

Several risk factors have previously been associated with increased morbidity following FPRS, such as older age (202). However, the association between age and mesh-related complications is uncertain. Higher incidence of exposure has been associated with both older (208) and younger age (211). Furthermore, several studies demonstrate increased pelvic pain in younger women after both urogynecologic and other surgery (192,212), similarly to our results. Our study also suggests a higher risk for complications among smokers, in agreement with similar studies, specifically linking smoking and mesh erosion (211), with pathogenetic mechanisms supporting this link (213). Concomitant hysterectomy has been associated with complications and mesh exposure by several studies (208,211). This was also the trend in our material (10 cases with concomitant hysterectomy, all with apical prolapse stage ≥ 2), but we did not observe any significant association between hysterectomy and manifestation of complications (OR=3.4, 95% CI=0.7-16.4).

In total, the addition of PSG to POP surgery adds to the risk for complications, obviously the risk for exposure and potentially other complications, such as pain and deformations. However, the extent to which the PSG alone is related to most complications is difficult to determine without a randomized study design. Accordingly, the use of PSG might have some positive impact on the risk for recurrence of prolapse but this effect does not appear to be considerable.

One major limitation of our study is the retrospective design, which also accounts for the significant heterogeneity in the study population considering the types of prolapse observed and the operations performed. Many of the participating women were examined by the operating gynecologist at the follow-up visit, potentially generating observer bias. The lack of standardized follow-up for complications and prolapse-related symptoms limits the evaluation of the complications profile and the subjective efficacy of PSG-augmented repairs. However, a subjective failure rate was estimated (12.9%) based on women's medical records. This percentage can naturally be higher because of women that

did not state their dissatisfaction or did it at some other institution. The three-month follow-up in our study was also relatively short but the participating women's medical records were reviewed for at least three years after the index operation without revealing additional complications while providing information about the long-term reoperation rate.

Conclusions

The first study shows that Ajust® is not inferior to the conventional mid-urethral slings regarding a three-year follow-up period. Our results, combined with the association of the failure of other mini-slings mainly with their inadequate fixation system, indicate that the presence of an efficient fixation in the obturator complex makes the potentially harmful penetration into deeper layers unnecessary. Further research is needed with longer follow-up periods and objective data to examine the possible benefits of mini-slings and gradually even the development of better devices.

The second and third study show that, despite a small decline in efficacy, MUS present good long-term results with an acceptable complications profile, as suggested by the participants' overall impression of improvement. The RP technique demonstrates significantly higher efficacy than the TO at ten years, with no difference between the two techniques concerning pelvic pain, sexual function, complications or reoperations due to sling-related complications. Preoperative urinary retention is a strong predictor for impaired efficacy and safety at 10 years, while postoperative retention constitutes the most common sling-related complication.

The fourth study demonstrates that pain- and urinary tract-related complications hold a central position in the range of complications following PSG-augmented POP surgery. Lower age, smoking and longer duration of surgery are identified as predictors for the development of complications, with lower age being associated with pain. The recurrence rates we recorded do not suggest a clear benefit from the use of PSG in prolapse surgery.

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