New insights into pelvic floor implants

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Chapter 1

General introduction

Background

In Urogynaecology, there is an ongoing search for new treatment strategies for pelvic organ prolapse (POP) and stress-urinary incontinence (SUI). Innovation and introduction of new interventions can have positive effect on healthcare, with better patient outcomes, improved efficiency or better diagnostics.[1] The risk of implementation of new interventions are negative outcomes that can potentially be harmful to patients. Therefore, new or modified existing techniques should be well evaluated before implementation in standard care. In this thesis we aim to evaluate (new) interventions in Urogynaecology. In the first part of this thesis we focus on polypropylene (PP) mesh as a treatment option for POP and in the second part we assess the effectiveness and safety of a new bulking injection agent; polydimethylsiloxane Urolastic® (PDMS-U) as an ambulatory treatment for SUI.

Part one: The use of (PP) mesh in pelvic reconstructive surgery.

POP is a common health disorder affecting up to 40% of women.[2] In 11% POP is symptomatic warranting treatment.[3]

POP can be treated conservatively by means of a pessary or pelvic floor physiotherapy or can be managed surgically. The lifetime risk of having an operation for POP or incontinence is approximately 11%.[4] Unfortunately the risk of recurrence is high. A population based registry study in Denmark showed a re-operation rate of 11.5% after 20 years of follow up in women that had been operated for POP, with the highest chance of having a reoperation (26.9%) in women that had their primary surgery before menopause.[5]

To reduce this risk of POP recurrence, operations with mesh implants have been introduced. In inguinal hernia repair this treatment strategy had been proven effective to prevent recurrence[6] and this has been extrapolated to pelvic floor surgery. Mesh induces a foreign body response and consequently new collagen and elastin are formed, making prolapse repair less dependent of the patient's own connective tissue.[7]

Mesh implants in pelvic reconstructive surgery

The PP meshes in pelvic floor repair were introduced in the '90s. Primarily for the abdominal approach and in 1996 and 2002 respectively, mesh for SUI and vaginal POP repair were cleared by the Federal Drug Administration (FDA) in the U.S.A.

After the introduction of procedures involving mesh prosthesis for pelvic organ surgery, mesh surgery has been incorporated into daily practice and many mesh procedures have been introduced to the market.

Outcome of vaginal mesh implants

The efficacy of vaginal mesh implants compared with native tissue repair has been subject of many trials. The group of Altman showed an improvement of objective and subjective outcome after vaginal mesh surgery in a group of women with mostly primary surgery for POP.[8]

Maher et al. performed a systematic review in 2016 that included 37 randomized controlled trials and 4023 women. This review showed that women having POP repair with mesh had less awareness of prolapse (RR 0.66, 95% confidence interval (CI) 0.54 to 0.81) after a follow up of 1 to 3 years, less repeat surgery for prolapse alone (RR 0.53, 95% CI 0.31 to 0.88), but more frequent repeat surgery when taking the combined outcome of POP, SUI or mesh exposure into consideration (RR 2.40, 95% CI 1.51 to 3.81). Women after vaginal mesh surgery had a higher chance of bladder injury (RR 3.92, 95% CI 1.62 to 9.50), and de novo SUI (RR 1.39, 95% CI 1.06 to 1.82). The overall quality of evidence was low to moderate. [9]

Mesh specific complications

The downside of mesh surgery is the fact that mesh implants can cause mesh specific complications. These complications include, mesh erosion (mesh protruding into the bladder or bowel) and mesh exposure (mesh protruding into the vagina). Pelvic pain and dyspareunia have also been attributed to mesh insertion, however these complaints have also been reported after native tissue repair. A study reporting on long-term outcomes comparing mesh with native tissue repair, observed non-significant differences in pain and dyspareunia after 7 years of follow up. Possibly pelvic surgery itself can be the causative factor for pain development.[10]

The incidence of mesh-related complications varies widely in literature and mesh-related complications were more common with the older, heavier PP mesh implants than with the newer ultralight meshes. [11-13] It has also been speculated on consumer websites and discussion platforms that PP implants can cause autoimmune inflammatory syndromes.

Treatment of mesh-related complications

The treatment approach of mesh-related complications depends on a variety of factors. These factors include the symptoms of the complication and the type of mesh product that has been inserted, e.g. midurethral sling, transvaginal mesh (TVM) or sacrocolpopexy (SCP).[14]

Symptomatology of mesh-related complications differs between patients. Some women have an exposure without any complaints, others have an exposure with pain or vaginal discharge and there is a group of women with pain without exposure. Moreover some women suffer from urogenital or rectovaginal fistula.

Asymptomatic women with an exposure do not have an indication for treatment. A conservative approach with in office resection of a mesh exposure and treatment with local estrogens have been done in some patients, but is mostly ineffective.[14]

If pain is the leading symptom (with and without a mesh exposure) surgery should be the treatment of choice often combined with pelvic floor physiotherapy, since muscle hypertonia is frequently part of the problem. The surgical approach varies amongst surgeons. Some advocate a total mesh removal to achieve symptom relief. Others believe that a partial mesh resection is sufficient to relief symptoms. The surgery can be performed vaginally in case of a TVM. When complaints are due to an abdominal mesh, an abdominal approach can be considered. Surgery can be challenging and will not always resolve the problem.

Regulations on mesh prosthesis
The mesh-related complication rates resulted in restrictive use of vaginal mesh implants. In 2008 the FDA issued a Public Health Notification (PHN) about mesh related complications and in 2011 it issued a safety communication, stating that mesh related complications are not rare and that there is a lack of evidence that vaginal mesh surgery is more effective than traditional repair.[15]

Following this PHN, the FDA issued post-market surveillance studies and reclassified surgical mesh for POP to a class 3 product. Consequently, pre-market approval to support safety and effectiveness has become mandatory for mesh implants for POP since 2016.

In response, the European Urology Association (EUA) and European Urogynaecological Association (EUGA) presented a consensus document. [16] In this document, it is concluded that the use of PP in SUI has good efficacy and safety, but alternative options must be considered. In POP, PP mesh should only be used in complex cases in which recurrence of the same compartment occurs and mesh should only be implanted by surgeons that are well trained and that work in referral centers.[16]

In 2019 the FDA ordered all manufacturers of vaginal mesh to stop manufacturing and distributing their mesh products, until three year follow up data will show a superiority of vaginal mesh over traditional repair.[17]

In the Netherlands, vaginal mesh has also been subject of debate, following the reports on mesh related complications. The Dutch Society of Gynaecology (NVOG) published notifications in 2012, 2014 and 2020 regulating the use of vaginal mesh implants in POP surgery. The Dutch inspection of health services (IGJ) performed their own investigation regarding these implants. In 2013, they concluded that vaginal mesh should be kept available, since many women might benefit from this treatment, but it should be used restrictive and the regulations of the NVOG should be incorporated.

In 2023 transvaginal mesh in the Netherlands is only available for women that consent to participate in a clinical trial.

Indications for mesh surgery
Even though there are mesh specific complications, there is a group of women that can benefit from vaginal mesh surgery. These are the women that have POP recurrence as stated by the EUA and EUGA and women with a collagen deficiency and chronically increased abdominal pressure or combination of the above as has been specified in a round table meeting of the International Urogynecological Association (IUGA) in 2010.[18] These women do not have many surgical treatment options left as native tissue repair has proven to be ineffective. They often have serious complaints, with a detrimental effect on quality of life.

Studies comparing vaginal mesh implants for POP with native tissue repair often include women with primary prolapse, instead of women with these specific indications as were specified by the IUGA in 2010. For example, the Prospect trial, a RCT performed in the UK in 2017 did not show benefit of mesh over native tissue repair in women with primary prolapse, [19] but primary prolapse is not an indication for mesh surgery and outcome in women with recurrence might be different.

In this thesis, we want to add to the evidence about vaginal mesh for POP in women with POP recurrence and to the evidence about mesh related complications and their treatment. We hypothesize that vaginal mesh should still be a viable treatment option in selected patients.

In summary, the aims for the first part of this thesis are:

1. *To explore long term complications of women treated with vaginal mesh surgery for pelvic organ prolapse*
2. *To evaluate health related quality of life (HrQol) in women after vaginal mesh surgery with and without mesh related complications*
3. *To assess the outcome of surgical interventions for complications of mesh surgery in pelvic reconstructive surgery*
4. *To evaluate whether there is a causal relationship between polypropylene implants and the development of a systemic inflammatory response or auto-immune disease*

Part two: Peri-urethral bulking injections (PBI) with PDMS-U for stress-urinary incontinence.

SUI is a significant clinical problem affecting approximately 20% of the female population.[20] This condition has a detrimental effect on quality of life.[21, 22] This negative impact can be improved substantially when urinary loss is reduced as a result of treatment.[23]

There are various treatment options. Conservative treatment modalities are behavioural therapy, pelvic floor muscle exercises, vaginal devices and pharmacological treatment.

Synthetic and autologous slings, colposuspension and bulking injections are the surgical alternatives.

Since the introduction of the synthetic mid-urethral sling (MUS) in the '90s, it became the gold standard for the surgical treatment of SUI, due to its minimal invasive approach and favourable outcome. However, the mesh debate did also have its effect on the MUS and now many Anglo-Saxon countries, refrain from MUS surgery. Hence, alternative, minimal invasive ambulatory treatment, like bulking injection therapy is becoming an interesting treatment option.

The hypothetical mechanism of action of bulking injection therapy is that the injected material in the urethral submucosa forms artificial cushions that improve urethral resistance to the urinary flow and hence improve continence.[24] To have a durable effect, bulking agents should ideally be non-immunogenic, biocompatible, causing a minimal inflammatory and fibrotic response, and the particles should be large enough to stay in place.[24]

Over the years, many bulking agents have been developed and used for the treatment of SUI. Some of these bulking agents caused (serious) complications and were therefore withdrawn from the market.[25] Other bulking agents, like Polyacrylamide Hydrogel have been used for many years and have been well evaluated. Polyacrylamide Hydrogel has been compared with the tension-free vaginal tape (TVT) in a non-inferiority clinical trial. [26] Women having a TVT were more satisfied and more often reported cure, but complications were seen less in the Polyacrylamide Hydrogel group and these women also reported a high satisfaction and cure rate. The authors concluded that Polyacrylamide Hydrogel can be offered as first line treatment for SUI, since satisfaction with this treatment is high and complications are scarce.[26] This lesser efficacy of bulking agents versus MUS has also been reported for other bulking agents.

This thesis focuses on bulking agent polydimethylsiloxane Urolastic® (PDMS-U) (Urogyn BV Nijmegen, the Netherlands). It had newly been introduced to the market, when the studies for this thesis were conducted. This bulking agent has the unique feature that

it polymerizes in situ, forming a uniform elastomer that adapts itself to the environment during injection. This implies that the bulk will not be absorbed by the body and will stay in position over time, theoretically increasing the chance of durability and efficacy.

In recent history, new treatment modalities have been introduced within Urogynaecology without proper evaluation of safety and efficacy. Therefore, we felt the need to evaluate this bulking agent prior to implementing its use into daily clinical practice.

In summary, the aims for the second part of this thesis are:

1. *To assess the efficacy and safety of PBI with PDMS-U in women with stress-urinary incontinence that are not optimal candidates for a MUS*
2. *To evaluate patients' satisfaction after PBI treatment with PDMS-U*
3. *To assess complications and re-interventions after PBI treatment with PDMS-U*
4. *To determine outcome during various time-after-treatment intervals*

Outline of the thesis

In **part one** of this thesis we focus on the outcome of mesh surgery for POP. We report on mesh-related complications, HrQol in women with and without mesh-related complications, the outcome of mesh revision surgery and we review the literature for potential causality of mesh implants and autoimmune syndromes.

In **Chapter** 2, we describe the results of a cross-sectional study in women that had vaginal mesh surgery for POP. We aim to explore the prevalence of long-term complications in these women and hereby improve future patient counselling.

In **Chapter 3,** we assess the effect of mesh related complications on HrQol in women that had vaginal mesh surgery for POP. HrQol is measured in women with and without mesh complications by use of standardized quality of life questionnaires (UDI-6, IIQ, DDI and PISQ-12). Complications are scored according to the IUGA complication classification.

In **Chapter 4,** we present the results of a cross-sectional study of women with mesh-related complications and the potential benefit of surgical mesh resection to alleviate symptoms.

In **Chapter 5,** we systematically review the literature to determine whether PP implants for inguinal, ventral hernia or pelvic floor surgery are associated with the development of systemic autoimmune syndromes.

In **part two** of this thesis we focus on the outcome of a bulking therapy for stress-urinary incontinence, PDMS-U (Urolastic®).

In **Chapter 6,** we present the results of a prospective study about subjective improvement in women that have been treated with PBI with PDMS-U and have a relative contra-indication for a MUS. Secondary outcome includes objective cure, disease specific quality of life and adverse events.

In **Chapter 7,** we evaluate patients' satisfaction with PBI with PDMS-U for SUI. Secondary outcomes are subjective cure, objective cure, severity of SUI symptoms, complications and re-intervention rate and disease-specific quality of life.

In **Chapter 8,** we discuss the main findings of this thesis and its implications for daily clinical practice and future research.

In **Chapter 9,** we summarize the results of the studies that have been performed for this thesis.

References

1 Leidraad Nieuwe Interventies in de Klinische Praktijk 2014 [Available from: https://www.demedischspecialist.nl/sites/default/files/Leidraad%20Nieuwe%20interventies%20in%20de%20klinische%20praktijk%20def.pdf2021.

2 M. C. Slieker-ten Hove, A. L. Pool-Goudzwaard, M. J. Eijkemans, R. P. Steegers-Theunissen, C. W. Burger, et al. *The prevalence of pelvic organ prolapse symptoms and signs and their relation with bladder and bowel disorders in a general female population*. Int Urogynecol J Pelvic Floor Dysfunct 2009;20(9):1037-45.

3 M. C. Slieker-ten Hove, A. L. Pool-Goudzwaard, M. J. Eijkemans, R. P. Steegers-Theunissen, C. W. Burger, et al. *Symptomatic pelvic organ prolapse and possible risk factors in a general population*. Am J Obstet Gynecol 2009;200(2):184 e1-7.

4 A. L. Olsen, V. J. Smith, J. O. Bergstrom, J. C. Colling & A. L. Clark. *Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence*. Obstet Gynecol 1997;89(4):501-6.

5 E. Lowenstein, L. A. Moller, J. Laigaard & H. Gimbel. *Reoperation for pelvic organ prolapse: a Danish cohort study with 15-20 years' follow-up*. Int Urogynecol J 2018;29(1):119-24.

6 I. L. Lichtenstein. *Herniorrhaphy. A personal experience with 6,321 cases*. Am J Surg 1987;153(6):553-9.

7 H. Patel, D. R. Ostergard & G. Sternschuss. *Polypropylene mesh and the host response*. Int Urogynecol J 2012;23(6):669-79.

8 D. Altman, T. Vayrynen, M. E. Engh, S. Axelsen, C. Falconer, et al. *Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse*. N Engl J Med 2011;364(19):1826-36.

9 C. Maher, B. Feiner, K. Baessler, C. Christmann-Schmid, N. Haya, et al. *Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse*. Cochrane Database Syst Rev 2016;2:CD012079.

10 A. L. Milani, A. Damoiseaux, J. IntHout, K. B. Kluivers & M. I. J. Withagen. *Long-term outcome of vaginal mesh or native tissue in recurrent prolapse: a randomized controlled trial*. Int Urogynecol J 2018;29(6):847-58.

11 M. I. Withagen, A. L. Milani, J. den Boon, H. A. Vervest & M. E. Vierhout. *Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse: a randomized controlled trial*. Obstet Gynecol 2011;117(2 Pt 1):242-50.

12 E. J. Stanford, R. D. Moore, J. P. Roovers, C. Courtieu, J. C. Lukban, et al. *Elevate anterior/apical: 12-month data showing safety and efficacy in surgical treatment of pelvic organ prolapse*. Female Pelvic Med Reconstr Surg 2013;19(2):79-83.

13 A. Gauthier, P. Ferry, P. Bertherat, R. De Tayrac & H. Fernandez. *Transvaginal treatment of anterior and apical genital prolapse using Restorelle(R) direct fix: An observational study of medium-term complications and outcomes*. J Gynecol Obstet Hum Reprod 2020;49(2):101674.

14 G. W. Cundiff, D. J. Quinlan, J. A. van Rensburg & M. Slack. *Foundation for an evidence-informed algorithm for treating pelvic floor mesh complications: a review*. BJOG 2018;125(8):1026-37.

15 Urogynecologic Surgical Mesh: Update on the safety and effectiveness of transvaginal placement for pelvic organ prolapse. : FDA, 2011.

16 C. R. Chapple, F. Cruz, X. Deffieux, A. L. Milani, S. Arlandis, et al. *Consensus Statement of the European Urology Association and the European Urogynaecological Association on the Use of Implanted Materials for Treating Pelvic Organ Prolapse and Stress Urinary Incontinence*. Eur Urol 2017;72(3):424-31.

17 Urogynecologic Surgical Mesh Implants U.S. Food & Drug Administration (FDA)2019 [Available from: https://www.fda.gov/medical-devices/implants-and-prosthetics/urogynecologic-surgical-mesh-implants2021.

18 G. W. Davila, K. Baessler, M. Cosson & L. Cardozo. *Selection of patients in whom vaginal graft use may be appropriate. Consensus of the 2nd IUGA Grafts Roundtable: optimizing safety and appropriateness of graft use in transvaginal pelvic reconstructive surgery.* Int Urogynecol J 2012;23 Suppl 1:S7-14.

19 C. M. Glazener, S. Breeman, A. Elders, C. Hemming, K. G. Cooper, et al. *Mesh, graft, or standard repair for women having primary transvaginal anterior or posterior compartment prolapse surgery: two parallel-group, multicentre, randomised, controlled trials (PROSPECT).* Lancet 2017;389(10067):381-92.

20 B. K. Hunskar S. *Epidemiology of urinary and faecal incontinence and pelvic organ prolapse. Incontinence volume 1, basic evaluation.* 3rd International Consultation on Incontinence edition 2005. Health publication Ltd 2005,. Paris, 2013.

21 C. H. van der Vaart, J. R. de Leeuw, J. P. Roovers & A. P. Heintz. *The effect of urinary incontinence and overactive bladder symptoms on quality of life in young women.* BJU Int 2002;90(6):544-9.

22 C. H. van der Vaart, J. R. de Leeuw, J. P. Roovers & A. P. Heintz. *[The influence of urinary incontinence on quality of life of community-dwelling, 45-70 year old Dutch women].* Ned Tijdschr Geneeskd 2000;144(19):894-7.

23 K. M. Gil, A. M. Somerville, S. Cichowski & J. L. Savitski. *Distress and quality of life characteristics associated with seeking surgical treatment for stress urinary incontinence.* Health Qual Life Outcomes 2009;7:8.

24 V. Kirchin, T. Page, P. E. Keegan, K. Atiemo, J. D. Cody, et al. *Urethral injection therapy for urinary incontinence in women.* Cochrane Database of Systematic Reviews 2012(2)

25 V. Kirchin, T. Page, P. E. Keegan, K. O. Atiemo, J. D. Cody, et al. *Urethral injection therapy for urinary incontinence in women.* Cochrane Database Syst Rev 2017;7:CD003881.

26 A. M. Itkonen Freitas, M. Mentula, P. Rahkola-Soisalo, S. Tulokas & T. S. Mikkola. *Tension-Free Vaginal Tape Surgery versus Polyacrylamide Hydrogel Injection for Primary Stress Urinary Incontinence: A Randomized Clinical Trial.* J Urol 2020;203(2):372-78.

Chapter 2

Reviewing patients following mesh repair; the benefits

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Gynecol Obstet Invest. 2017;82(6):575-581

Abstract

Background/aims

The use of synthetic mesh implants for vaginal prolapse surgery is still a subject of debate due to safety concerns. We aimed to explore long-term complications of all women treated with mesh surgery for pelvic organ prolapse (POP) in our center.

Methods

This is a cross-sectional study of 188 women who underwent vaginal mesh surgery in a Dutch University Hospital between 2007 and 2012. The prevalence of mesh exposure, pain symptoms and patient satisfaction has been documented.

Results

Vaginal mesh surgery was performed in 188 women - in 147 (78%) because of recurrent POP. After a median follow-up of 40 months (range 12-76 months), 11 women (6%) had a symptomatic exposure of whom 8 women underwent surgery. Nine women (5%) had de novo pain following mesh surgery and in 3 women (2%) this symptom was persistent despite treatment. Eighty-six percent of the responders were satisfied about their treatment.

Conclusion

With this study, we showed that performing a total mesh recall is feasible. The prevalence of persisting symptomatic exposure and persisting pain symptoms was low in our population. Most of the complications we found were treatable. This is also reflected in the high overall satisfaction rate.

Introduction

Prolapse surgery is a commonly performed procedure. Due to the high recurrence rates, a shift towards the use of synthetic meshes has occurred. Previous studies have shown better objective outcomes of prolapse surgery using synthetic mesh[1, 2] and in 2011, a large randomised controlled trial (RCT) also showed better subjective outcomes.[3]

However, during the past years, we also learnt that the higher success rates of mesh surgery should be balanced against the risk on mesh-specific complications.

Treatment of these mesh-specific complications is difficult as complete mesh removal is technically challenging and does not guarantee relief from symptoms. Extensive counselling about the risks of vaginal mesh surgery is therefore crucial. Since we know from previous literature that many mesh-specific complications are related to a specific type of mesh kit and because these complications might also depend on the experience of the surgeon and infrastructure of the hospital, we thought it important to evaluate the results of the meshes implanted in our own center.[4]

Our objective was to explore the prevalence of mesh-specific complications in our center and thereby improve future patient counselling.

Materials and Methods

A cross-sectional study was performed in the Academic Medical Center (AMC) in Amsterdam in the Netherlands. The Medical Ethics Review Committee of the AMC in Amsterdam judged that the Medical Research Involving Human Subjects Act does not apply to this study.

All women operated between 2007 and 2012 with a vaginal synthetic mesh procedure were asked to participate in this study. Indications for vaginal synthetic mesh implants were recurrence of POP (defined as recurrence of symptomatic prolapse at or beyond the hymen in the operated compartment), women with a posterior compartment prolapse after previous vaginal hysterectomy or women participating in an observational study or RCT evaluating primary vaginal synthetic mesh surgery.[5-7] Implantation of polypropylene mesh started in our hospital in 2007 with Perigee™ and Apogee™ (Astora Women's Health, Eden Prairie, USA). From 2008 onwards, Elevate® Anterior and Elevate® Posterior mesh kits (Astora Women's Health, Eden Prairie, USA) were implanted as well.

The procedures were performed under general anaesthesia or spinal analgesia. Patients received a single dose of intravenous prophylactic antibiotics during surgery and postoperative prophylaxis for deep vein thrombosis. A 14 French Foley indwelling

catheter with a 10-mL balloon was used to drain the bladder after surgery and all women had a vaginal pack insertion after surgery. The catheter and vaginal packing was removed on the morning of the first postoperative day. After removal of the catheter, the first micturition was measured and a bladder scan was performed to evaluate if a woman had urinary retention of more than 150 mL. In that case, clean intermittent catheterisation was started.

From all patients fulfilling our inclusion criteria, a chart review was performed. All patients received a letter notifying them of the study. Patients could opt out by sending an email if they did not wish to be contacted. Within 2 weeks after receiving the letter, the patients were called by one of the investigators asking them for their consent to participate in the study. All patients were invited to visit the clinic for a study visit.

During the study visit, women were asked the following questions regarding their treatment: (1) “How satisfied were you with your treatment?” Women could answer on a 5-level Likert scale, ranging from “very satisfied” to “not satisfied.” Women were documented as satisfied, if they answered very satisfied or satisfied. (2) “Would you recommend this treatment to a friend or colleague?”

After answering these questions, an interview was performed by a gynaecologist. The investigator was not blinded to the previously performed mesh procedure and in some cases, the evaluator participated in the index surgery. During the interview, the following items were discussed: current symptoms of pelvic floor dysfunction or mesh-related complications such as pain or exposure, re-interventions for pelvic floor dysfunction or complications related to surgery and adjuvant treatment (medication, surgery or physiotherapy) for pelvic floor dysfunction or mesh-related complications that was started after surgery.

After the interview, patients underwent pelvic examination to evaluate mesh complications. During this exam, the vagina was palpated to identify the presence and location of mesh exposure and to assess whether palpation of the mesh provoked pain.

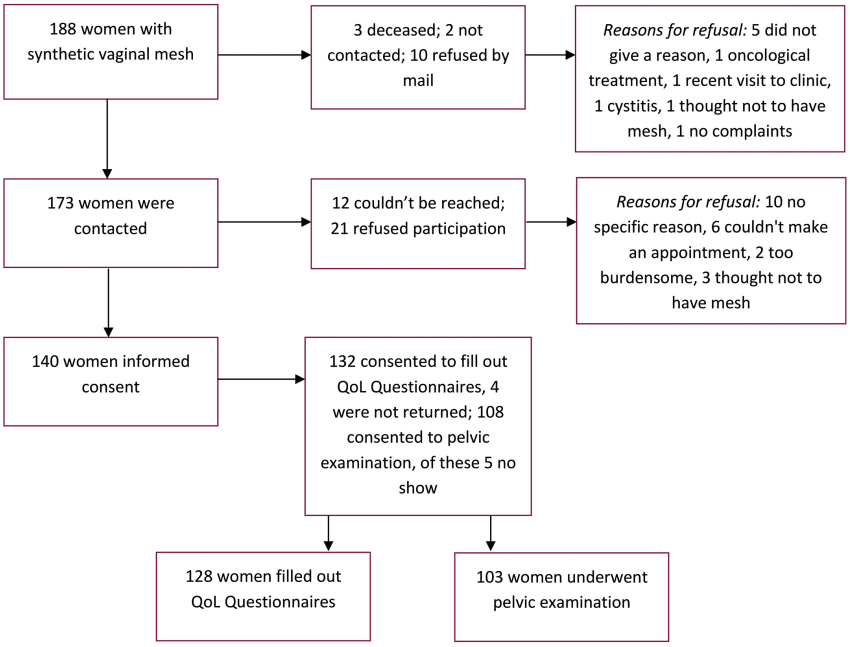
Mesh-related complications observed during pelvic examination were scored using the joint IUGA/ICS classification.[8]

In those women who reported pain during the study visit, their medical chart was checked whether they had pain symptoms prior to mesh surgery.

Data was analysed using IBM SPSS Statistics 22. Demographic and baseline characteristics were summarized using standard descriptive methods. Percentages of adverse events were calculated.

Results

During the study period, vaginal mesh surgery was performed in 188 women. For all these women, an extensive chart review was performed. Figure 1 shows the distribution of patients that filled out the quality-of-life questionnaires and had a pelvic examination complementary to the chart review.



Median follow-up was 40 months (range 12-76 months). Baseline characteristics of our study population are shown in Table 1. Most women had undergone one or more prolapse procedures in the past. Ten women had a history of vaginal mesh surgery.

In Table 2, the performed surgical procedures and short-term complications are depicted.

In our study population, the most common long-term complications were pain and mesh exposure. These complications were surgically treated in 17 of the 188 women (9%) - in 9 women because of pain caused by the mesh implant and in the other 8 because of a symptomatic mesh exposure.

Pain symptoms were reported by 23/188 (12%) women. Nine of them developed pain after mesh surgery (5%), the other 14 women already had pain complaints prior to the mesh procedure. Women with pain symptoms were treated by pelvic floor muscle therapy or surgically by mesh removal. Of the 9 women who had pain as a newly developed symptom, 3/188 (2%) had persisting pain regardless of treatment.

Table 1. Baseline characteristics of the study population

Total	N=188	
Age, years, mean (SD)	60.2	(11.4)
BMI, kg/m^2, mean (SD)	26.4	(3.6)
Mesh performed due to recurrence	147	(78.2)
Surgical history*		
Hysterectomy abdominal	19	(10.1)
Hysterectomy vaginal	82	(43.6)
Hysterectomy laparoscopic	1	(0.5)
Vaginal prolapse surgery (i.e. AC, PC, SSLF or a combination)	110	(58.5)
Abdominal prolapse surgery	13	(6.9)
Stress incontinence surgery	17	(9.0)
Previous mesh surgery	10	(5.3)
Findings at pelvic examination		
Anterior compartment prolapse		
Missing	24	(12.8)
None	11	(5.9)
Stage 1	19	(10.1)
Stage 2	91	(48.4)
Stage 3	43	(22.9)
Apical compartment prolapse		
Missing	31	(16.5)
None	89	(47.4)
Stage 1	20	(10.6)
Stage 2	36	(19.1)
Stage 3	12	(6.4)
Posterior compartment prolapse		
Missing	31	(16.5)
None	45	(24)
Stage 1	47	(25)
Stage 2	48	(25.5)
Stage 3	17	(9)

Data are expressed as absolute numbers (percentage).
*some patients had more than 1 previous procedure.
AC, anterior colporrhaphy; PC, posterior colporrhaphy;
SSLF, sacrospinous ligament fixation

Table 2. Surgical procedures and short-term complications

Total	N=188	
Type of mesh		
Perigee	51	(27.1)
Apogee	4	(2.1)
Elevate anterior	63	(33.5)
Elevate posterior	65	(34.6)
Mesh in multiple compartments	5	(2.7)
Blood loss, mL, median (range)	50	(0-500)
Hospital stay, days, median (range)	1	(0-5)
Concomitant surgical procedures		
TVT	13	(6.9)
Perineoplastia	15	(8.0)
Posterior colporrhraphy	4	(2.1)
Enterocele correction	8	(4.3)
Anterior colporrhaphy	7	(3.7)
Sacrospinous ligament fixation	11	(5.9)
Portio amputation	1	(0.5)
Revision perigee	1	(0.5)
Complications during surgery		
Bladder lesion	1	(0.5)
Bleeding > 500 mL	1	(0.5)
Complications during hospital stay *		
Bleeding vaginal wall	6	(3.2)
Cystitis	18	(9.6)
Wound infection	3	(1.6)
Abcess	1	(0.5)
Urinary retention	15	(8.0)
Hematoma	4	(2.1)
Complications 6 weeks after surgery		
Exposure	11	(5.9)
Dyspareunia	2	(1.1)
Pain	12	(6.4)
Cystitis	9	(4.8)
Urinary retention	2	(1.1)

Data are expressed as median (range], or absolute numbers (percentage).

From the 23 women with pain symptoms, 4 women also had a mesh exposure. In total, 26 women (14%) had a mesh exposure somewhere during the postoperative follow-up. In 10 women, this was first noticed 6 weeks postoperative, and in 8 women, this was noticed during the extra visit for this study. Most of these exposures were asymptomatic (n = 15) and therefore treated conservatively with topical oestrogens or excision of the exposure in the outpatient center. Eleven women had a symptomatic exposure (6%), of whom 8 women underwent an operative correction of the mesh exposure and 3 were conservatively treated. After treatment, 1 woman had a persisting symptomatic exposure (0.5%). Details of the complications categorized according to the joint IUGA/ICS classification are summarized in Table 3.

As complication rates might differ between the different types of mesh, we explored if this was also the case in our study population. Pain symptoms appeared to be more common in women after surgery with elevate posterior than after surgery with the other meshes; however, this was not statistically significant (p = 0.06).

All women were asked whether they were satisfied with their treatment for vaginal prolapse by mesh implantation. Eighty-six percent of the responders were satisfied and 78% would recommend vaginal mesh surgery to a friend or colleague.

Table 3. Frequency table of the International Urogynecology Association/ International Continence Society scoring system for mesh related complications.

Category	Total in Category	Code	Frequency	Description
No complication	144			
Category 1	17	1BcT4S2	1	Wrinkling or shrinkage of the mesh, pain during sexual intercourse
		1BbT4S3	1	Wrinkling or shrinkage of the mesh, provoked pain only
		1BcT2Smissing	1	Wrinkling or shrinkage of the mesh, pain during sexual intercourse
		1BcT3S1	1	Wrinkling or shrinkage of the mesh, pain during sexual intercourse
		1BcT3S4	1	Wrinkling or shrinkage of the mesh, pain during sexual intercourse
		1BcTmissingSmissing	1	Wrinkling or shrinkage of the mesh, pain during sexual intercourse
		1BdT3S4	1	Wrinkling or shrinkage of the mesh, pain during physical activities
		1BeT1S3	1	Wrinkling or shrinkage of the mesh, spontaneous pain
		1BeT2S3	1	Wrinkling or shrinkage of the mesh, spontaneous pain
		1BeT2S5	1	Wrinkling or shrinkage of the mesh, spontaneous pain
		1BeT3S3	1	Wrinkling or shrinkage of the mesh, spontaneous pain
		1BeT3S4	1	Wrinkling or shrinkage of the mesh, spontaneous pain
		1BeT3S5	1	Wrinkling or shrinkage of the mesh, spontaneous pain
		1BeT4S2	1	Wrinkling or shrinkage of the mesh, spontaneous pain
		1BeT4S3	1	Wrinkling or shrinkage of the mesh, spontaneous pain
		1BeT4S5	1	Wrinkling or shrinkage of the mesh, spontaneous pain
		1BeTmissingS5	1	Wrinkling or shrinkage of the mesh, spontaneous pain
Category 2	13	2AaT2S1	1	Asymptomatic mesh exposure <1cm
		2AaT2S2	1	Asymptomatic mesh exposure <1cm
		2AaT4S2	4	Asymptomatic mesh exposure <1cm
		2AaT4S8	1	Asymptomatic mesh exposure <1cm
		2BmissingT4S1	1	Symptomatic mesh exposure < 1cm, pain unspecified

Table 3. Frequency table of the International Urogynecology Association/ International Continence Society scoring system for mesh related complications. *(continued)*

Category	Total in Category	Code	Frequency	Description
		2BaT4S1	1	Symptomatic mesh exposure <1cm, no pain, bleeding complaints
		2BaT4S2	1	Symptomatic mesh exposure <1cm, no pain, bleeding complaints
		2BbT4S1	1	Symptomatic mesh exposure <1cm, provoked pain only
		2BbT4S2	1	Symptomatic mesh exposure <1cm, provoked pain only
		2BeT2Smissing	1	Symptomatic mesh exposure <1cm, spontaneous pain
Category 3	8	3AaT2S2	1	Asymptomatic mesh exposure > 1cm
		3AaT4S2	3	Asymptomatic mesh exposure > 1cm
		3AaT4Smissing	1	Asymptomatic mesh exposure > 1cm
		3BaT2S1	2	Symptomatic mesh exposure > 1cm, no pain, bleeding complaints
		3BaT4S1	1	Symptomatic mesh exposure > 1cm, no pain, bleeding complaints
Category 4	0			
Category 5	1	5BeT3S4	1	Compression of bowel with spontaneous pain
Category 6	0			
Category 7	0			
Category 2/3	5	AaT2S1	1	Asymptomatic exposure, size not specified
		AaT4S1	1	Asymptomatic exposure, size not specified
		AaT4Smissing	1	Asymptomatic exposure, size not specified
		BaT2S1	1	Symptomatic mesh exposure, size not specified, no pain, bleeding complaints
		BcT2S2	1	Symptomatic mesh exposure, size not specified, pain during sexual intercourse

Discussion

We explored complications of all women who underwent a vaginal mesh procedure in our hospital. This total recall turned out feasible. Eleven women (6%) had a symptomatic exposure of whom 8 women underwent surgery. Nine women (5%) had de novo pain following mesh surgery and in 3 women (2%) this symptom was persistent despite treatment. Most women were satisfied about their treatment and would recommend a mesh procedure to a friend or colleague.

The most common mesh-specific complication observed in our study was exposure. Exposure rates in literature vary considerably from 5 to 20%.[9, 10]

Most of this variation might be explained by the method of follow-up and the type of exposures reported. Studies with a high exposure rate mostly have an intensive follow-up schedule and report all exposures, not only the symptomatic ones. Other studies with lower exposure rates report short-term follow up, or only symptomatic exposures.

In our study, we found an overall exposure rate of 14%; however, less than half of these exposures were symptomatic and warranted treatment. Non-symptomatic exposures can be treated either conservatively by in-office excision of the exposed mesh combined with vaginal oestrogen or no treatment at all.[11]

Therefore, the clinical relevance of a non-symptomatic exposure is questionable. We think that the 6% chance of developing a symptomatic exposure, which needs further treatment, should be incorporated into patient counselling, together with the 0.5% chance that this treatment is not effective.

The other important, sometimes irreversible, complication after mesh augmented pelvic reconstructive surgery is pain. Our postoperative pain rate (including dyspareunia) of 12%, with a de novo pain rate of 5% is in line with earlier reports.[2, 4, 11] Fortunately, most of the newly developed pain symptoms could be treated; however, in 2%, pain was persistent despite treatment. This should be mentioned during counselling.

From previous literature, we already know that preoperative pain is a risk factor for postoperative pain.[4] We confirmed that most women with pain symptoms had pain symptoms before surgery. In these patients, persistent pain after mesh surgery is probably mesh unrelated, since the pain was present beforehand, and therefore, can be wrongly attributed to the mesh implant. In women already experiencing pain symptoms, we advocate that the use of mesh be discouraged.

We explored whether complications were specific to the mesh type; however, groups were too small to draw conclusions on differences in complication rates between the types of mesh.

Interestingly, even though mesh-specific complications were not uncommon in our center, the majority of patients were still satisfied with this treatment (86% in our population). The improvement and overall success rates (75-82%) of other single-center reports with long-term follow-up are in line with this finding.[12, 13]

Refusal of participation may have provoked selection bias. Fifteen women did not want to elucidate why they refused participation, while the other women had variable reasons for not wanting to participate. None of the patients reported that dissatisfaction was the reason for not participating. By carefully examining all medical files (responders and non-responders), we have tried to complete follow-up. Second, bias could have occurred as part of the interviews and exams were performed by the surgeon who also performed the mesh surgery and the investigator was not blinded to the performed treatment. It is known that patients who are interviewed by their own healthcare provider may be overoptimistic about treatment outcome. We selected the surgeons as investigators in part of the exams, since they were the most experienced team members to accurately assess the outcome of mesh surgery.

An important strength of performing a cross-sectional study is that it shows what the complication rates are in daily practice. RCTs have stringent selection criteria affecting outcome. For example, multiple trials only included patients with primary prolapse repair, whereas mesh is often used in patients with recurrent prolapse.[1, 14] Theoretically, patients with recurrence of prolapse have a higher risk of complications because they already have scar tissue vaginally, which can influence the healing process or make them prone to have exposures.

With this study, we showed that performing a total mesh recall is feasible. The prevalence of persisting symptomatic exposure and persisting pain symptoms was low in our population. Most of the complications we found were treatable. This is also reflected in the high overall satisfaction rate. We encourage our colleagues worldwide to perform a mesh recall to help improve detection and treatment of mesh-specific complications. For our own center, we now have more accurate numbers to counsel patients on the risk of mesh-specific complications. We are of the opinion that these numbers give a better reflection of daily practice than the numbers presented in studies, as most of the studies lack long-term follow-up and only include women for primary POP surgery without any comorbidity. These numbers are now incorporated in our patient counselling.

References

1 A. Vollebregt, K. Fischer, D. Gietelink & C. H. van der Vaart. *Primary surgical repair of anterior vaginal prolapse: a randomised trial comparing anatomical and functional outcome between anterior colporrhaphy and trocar-guided transobturator anterior mesh*. BJOG 2011;118(12):1518-27.

2 M. I. Withagen, A. L. Milani, J. den Boon, H. A. Vervest & M. E. Vierhout. *Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse: a randomized controlled trial*. Obstet Gynecol 2011;117(2 Pt 1):242-50.

3 D. Altman, T. Vayrynen, M. E. Engh, S. Axelsen, C. Falconer, et al. *Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse*. N Engl J Med 2011;364(19):1826-36.

4 M. I. Withagen, M. E. Vierhout, J. C. Hendriks, K. B. Kluivers & A. L. Milani. *Risk factors for exposure, pain, and dyspareunia after tension-free vaginal mesh procedure*. Obstet Gynecol 2011;118(3):629-36.

5 S. Thijs, J. Deprest, D. de Ridder, F. Claerhout, J. Roovers. A Randomized controlled trial of anterior colporraphy and Perigee™ as a primary surgical correction of symptomatic cystocele. Annual meeting ICS/IUGA; 2010; Toronto.

6 E. J. Stanford, R. D. Moore, J. P. Roovers, C. Courtieu, J. C. Lukban, et al. *Elevate anterior/apical: 12-month data showing safety and efficacy in surgical treatment of pelvic organ prolapse*. Female Pelvic Med Reconstr Surg 2013;19(2):79-83.

7 J. C. Lukban, J. P. Roovers, D. M. Vandrie, T. Erickson, S. Zylstra, et al. *Single-incision apical and posterior mesh repair: 1-year prospective outcomes*. Int Urogynecol J 2012;23(10):1413-9.

8 B. T. Haylen, R. M. Freeman, J. Lee, S. E. Swift, M. Cosson, et al. *International Urogynecological Association (IUGA)/International Continence Society (ICS) joint terminology and classification of the complications related to native tissue female pelvic floor surgery*. Neurourol Urodyn 2012;31(4):406-14.

9 X. Deffieux, R. de Tayrac, C. Huel, J. Bottero, A. Gervaise, et al. *Vaginal mesh erosion after transvaginal repair of cystocele using Gynemesh or Gynemesh-Soft in 138 women: a comparative study*. Int Urogynecol J Pelvic Floor Dysfunct 2007;18(1):73-9.

10 J. N. Nguyen & R. J. Burchette. *Outcome after anterior vaginal prolapse repair: a randomized controlled trial*. Obstet Gynecol 2008;111(4):891-8.

11 P. J. Culligan, P. M. Littman, C. G. Salamon, J. L. Priestley & A. Shariati. *Evaluation of a transvaginal mesh delivery system for the correction of pelvic organ prolapse: subjective and objective findings at least 1 year after surgery*. Am J Obstet Gynecol 2010;203(5):506 e1-6.

12 D. Karmakar, L. Hayward, J. Smalldridge & S. Lin. *Vaginal mesh for prolapse: a long-term prospective study of 218 mesh kits from a single centre*. Int Urogynecol J 2015

13 H. F. Bontje, G. van de Pol, H. J. van der Zaag-Loonen & W. A. Spaans. *Follow-up of mesh complications using the IUGA/ICS category-time-site coding classification*. Int Urogynecol J 2014;25(6):817-22.

14 M. Rudnicki, E. Laurikainen, R. Pogosean, I. Kinne, U. Jakobsson, et al. *Anterior colporrhaphy compared with collagen-coated transvaginal mesh for anterior vaginal wall prolapse: a randomised controlled trial*. BJOG 2014;121(1):102-10; discussion 10-1.

Chapter 3

Effects of mesh-related complications in vaginal surgery on quality of life

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Abstract

Introduction and hypothesis

Vaginal mesh surgery is subject of debate due to the impact of mesh-related complications on patient's lives. Not all of these complications are symptomatic. Restoration of the anatomy and improvement of pelvic floor function as a result may counter the experienced discomfort related to adverse events. We hypothesized that health-related quality of life (HR-QoL) is comparable in women after vaginal mesh surgery regardless of the presence or absence of a mesh-specific complication.

Methods

This was a cross-sectional study of 128 women who had vaginal mesh surgery in a Dutch university hospital between 2007 and 2012. HR-QoL was measured in women with and without mesh complications using standardized QoL questionnaires; Urogenital Distress Inventory-6 (UDI-6), Incontinence Impact Questionnaire (IIQ), Defecation Distress Inventory (DDI), and Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-12). Complications were scored according to the International Urogynecological Association (IUGA) complication classification. Comparisons between groups were performed with Student's t test and analysis of variance (ANOVA) test.

Results

In 29 (23%) women, a mesh-related complication occurred. The domain scores of the UDI-6, DDI, IIQ, and PISQ showed no statistically significant differences between women with and without a mesh-related complication. A post hoc analysis showed similar HR-QoL for those in whom the complication had been resolved and those with persistent symptoms of the complication.

Conclusion

Mesh surgery imposes specific complications. When counselling patients about the potential adverse events related to vaginal mesh surgery, it is important to inform them that mesh-related complications do not negatively affect QoL related to micturition, defecation, and sexual functioning.

Introduction

The treatment of pelvic organ prolapse (POP) is challenging, since the recurrence rate after surgical treatment is high. It has been shown that 29% of women that undergo an operation for POP and/or urinary incontinence will have a reoperation.[1] In women with POP recurrence, a reoperation rate of 11.5% has recently been reported in a large Danish Cohort study after 20 years of follow up.[2]

Polypropylene mesh was introduced as the possible solution to this high recurrence risk. The mesh induces a foreign body response and as part of that, new collagen and elastin are formed, consequently making the repair less dependent on the patient's own connective tissue[3]. Altman and co-workers have shown that both objective and subjective cure are better following vaginal mesh surgery as compared to native tissue repair. They reported a re-intervention rate for mesh related complications of 3.2%, but a recent multicenter randomized controlled trial (RCT) performed in the UK, reported a re-operation risk for mesh-related complications in 9% of the patients. [4, 5] The risk on mesh-related complications was one of the main reasons for the FDA to issue Public Health Notifications in 2008 and 2011 in which they advise the restrictive use of mesh and to optimize patient counselling regarding the possible adverse events of mesh surgery.[6]

Interestingly enough, it has not yet been studied what the effects of mesh-related complications on the patient's quality of life are. Not all complications are symptomatic and the advantages of restored anatomy and associated improved pelvic floor function may outweigh the discomfort related to surgery-related adverse events.

To optimize patient counselling about mesh-specific adverse events, as recommended by the FDA and professional organizations, information about the effects of such complications on quality of life in women is highly relevant. We hypothesized that health related quality of life (HrQol) is comparable in women after vaginal mesh surgery regardless of the presence or absence of a mesh specific complication.

Materials and Methods

We performed a cross-sectional study in the Academic Medical Center (AMC) in Amsterdam, the Netherlands. The medical ethics committee of the AMC judged that the Medical Research Involving Human Subjects Act does not apply to this study, since the study only involved completing questionnaires and one additional pelvic floor examination that can be justified by the fact that mesh-related complications, if present, can be managed.

Population
Women who have had a vaginal polypropylene mesh procedure in the AMC between 2007 and 2012 were contacted by letter and asked for consent to participate in this study. Within 2 weeks after the letter had been send, women were contacted by phone and asked if they were willing to participate in the study. Women that did not want to be contacted could opt out by sending an email.

Indications to perform vaginal mesh surgery were recurrence of POP, women with a posterior vaginal wall prolapse after previous vaginal hysterectomy or women participating in studies to evaluate the outcomes of vaginal mesh surgery.[7-9]

Procedures
Mesh kits implanted during the study period were Perigee™, Apogee™, Elevate® Anterior and Elevate® Posterior, (Astora Women's Health, Eden Prairie, US). The procedures were performed under general anaesthesia or spinal analgesia. The procedures were performed as indicated by the manufacturer of the mesh implant.

Outcome measurements
We measured Hr-QoL in women following mesh surgery, defined as QoI related to micturition, defecation and sexual functioning.

This was assessed using the Dutch versions of the following validated Hr-QoI questionnaires: Urogenital Distress Inventory (UDI-6), Incontinence Impact Questionnaire (IIQ), Defecation Distress Inventory (DDI), Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-12). Women were asked to fill out the questionnaires prior to their clinical examination.

1. The UDI-6 assesses the presence and experienced bother of pelvic floor symptoms associated with lower urinary tract dysfunction. Scores are divided into 3 domains: irritative, stress and obstructive/ discomfort symptoms. Scores range from 0-100 per domain, with 0 identifying patients who experience no bother related to micturition symptoms and 100 identifying patients who experience maximal bother.[10 11]

2. The IIQ measures the impact of UI on different aspects of QoL. The questions are divided into four domains: travel, physical activity, social relationships, and emotional health. Subscale scores range from 0 to 100. The total score is given by the sum of all subscale scores, ranging from 0 to 400. A higher score implicates more bother.[12]

3. The DDI assesses the presence and experienced bother of defecatory symptoms. The questions are divided into four distinct domains: constipation, painful defecation, fecal incontinence and flatus incontinence.[13] Each domain score ranges from 0-100, with 0 identifying patients without any defecatory symptoms and 100 identifying

patients who encounter all possible symptoms and experience these as maximal bothersome.[14]

4. The PISQ-12 assesses sexual functioning in women with POP and/or UI and addresses physical, behavioural–emotive, and partner-related aspects of sexual functioning. The sum score ranges from 0 to 48, with a higher score indicating better sexual functioning.[15]

To assess the presence or absence of a mesh-related complication, participators were invited for a study visit during which their history was taken and a gynaecologist performed a pelvic examination. The investigator was not blinded to the previously performed mesh procedure, and in some cases, the evaluator participated in the index surgery. During this visit, current symptoms of pelvic floor dysfunction or mesh-related complications such as pain or exposure, re-interventions for pelvic floor dysfunction, or complications related to surgery and adjuvant treatment (medication, surgery, or physiotherapy) were discussed. Complications were scored according to the IUGA classification of complications related directly to the insertion of prostheses or grafts in urogynaecological surgery.[16]

Statistical analysis

Patient demographic and baseline characteristics were summarized using standard descriptive methods. HR-QoL was calculated by analysing the outcome of the validated QoL questionnaires. Comparisons of the UDI-6, IIQ, DDI, and PISQ-12 between women with and without a mesh complication were performed using the independent samples t test. Comparison between more than two groups were performed with the analysis of variance (ANOVA) test.

Post hoc analyses were performed to evaluate if there were any statistically significant differences between women in which the complication was still present or had been resolved. Data was analysed using IBM SPSS Statistics 23.

Results

The response rate was 68% (128/188 patients). Of these women, ten refused to be contacted by mail, three were deceased, 14 could not be reached, and 21 refused participation after they had been contacted by phone. Of the 140 women who consented to participate, 128 actually filled out the questionnaires. Most women did not give a specific reason for not being willing to participate. Baseline characteristics of respondents are shown in Table 1. Women who filled out the questionnaire and visited the clinic were significantly younger at the time of surgery than women who did not want to participate ($p = 0.04$). Most women (78%) had a mesh procedure because of recurrence. Almost all women who underwent primary mesh surgery participated in a clinical study. Ten women had had a previous mesh implantation for POP.

From the respondents, 29 women (23%) had a complication during follow-up, 17 had an exposure, and 12 had long-lasting pain without exposure. The IUGA classification of these complications is depicted in Table 2.

TABLE 1. Baseline Characteristics of the study population

Patient demographics	No complication n = 99	Complication n = 29	p-value
Age (years) *mean (SD)*	60 (11)	57 (9.3)	0.17
BMI *mean (SD)*	26 (3.6)	27 (3.8)	0.09
Parity *mean (SD)*	2.3 (0.8)	2.6 (1.3)	0.28
Follow up (months) *median (range)*	39 (17.5)	46 (19.5)	0.12
Surgical history			
Hysterectomy vaginal	41 (41%)	13 (45%)	0.27
Hysterectomy laparoscopic	0	1 (3%)	
Hysterectomy abdominal	11 (11%)	2 (7%)	
Type of mesh			
Perigee	19 (19%)	8 (28%)	0.02
Apogee	0	2 (7%)	
Elevate anterior	44 (44%)	9 (31%)	
Elevate posterior	35 (35%)	8 (28%)	
Mesh in multiple compartments	1 (1%)	2 (7%)	

Data are expressed as mean (SD), median (range) or absolute numbers (%)
SD: standard deviation. BMI body mass index
Significance cut-off p<0.05

TABLE 2. Frequency of the international Urogynecology Association/ International Continence Society scoring system for mesh-related complications

Category	**Total in Category**	**Code**	**Frequency**	**Description**
Category 1	12	1BcT2S8	1	Symptomatic, pain during sexual intercourse
		1BcT3S1	1	Symptomatic, pain during sexual intercourse
		1BcT4S2	1	Symptomatic, pain during sexual intercourse
		1BcT8S8	1	Symptomatic, pain during sexual intercourse
		1BdT3S4	1	Symptomatic, pain during physical activities
		1BeT1S3	1	Symptomatic, spontaneous pain
		1BeT2S3	1	Symptomatic, spontaneous pain
		1BeT3S4	1	Symptomatic, spontaneous pain

TABLE 2. Frequency of the international Urogynecology Association/ International Continence Society scoring system for mesh-related complications *(continued)*

Category	Total in Category	Code	Frequency	Description
		1BeT4S2	1	Symptomatic, spontaneous pain
		1BeT4S3	1	Symptomatic, spontaneous pain
		1BeT4S5	1	Symptomatic, spontaneous pain
		1BeT8S5		Symptomatic, spontaneous pain
Category 2	10	2AaT2S1	1	Asymptomatic mesh exposure <1cm
		2AaT4S2	3	Asymptomatic mesh exposure <1cm
		2AaT4S8	1	Asymptomatic mesh exposure <1cm
		2B8T4S1	1	Symptomatic mesh exposure < 1cm
		2BaT4S1	1	Symptomatic mesh exposure < 1cm, no pain
		2BaT4S2	1	Symptomatic mesh exposure < 1cm, no pain
		2BbT4S1	1	Symptomatic mesh exposure < 1cm, provoked pain
		2BbT4S2	1	Symptomatic mesh exposure < 1cm, provoked pain
Category 3	5	3AaT4S2	3	Asymptomatic mesh exposure >1cm
		3BaT2S1	1	Symptomatic mesh exposure>1cm, no pain
		3BaT4S1	1	Symptomatic mesh exposure>1cm, no pain
	2	8AaT2S1	1	Asymptomatic mesh exposure, exposure size unknown
		8BaT2S1	1	Symptomatic mesh exposure, exposure size unknown

Functional outcome of women with and without a complication during follow-up is compared in table 3. UDI, DDI, and IIQ scores did not significantly differ between groups. Post hoc analyses showed no statistically significant differences between women in whom the complication was still present or had been resolved.

From respondents, 72 (56%) women reported being sexually active; they were significantly younger [54.5 years (SD 8.9) vs 64.8 years (SD 9.4); p = 0.00). In women with a mesh-related complication, 62% (18/29) were sexually active vs 55% in the group of women without a complication. Of women in whom the complication was still present during the follow-up visit, 63% was sexually active.

Whether refraining from sexual activity was caused by mesh complications is not known. Table 4 depicts the replies of sexually active women with and without complications. In the whole group of sexually active women, 69% was very or reasonably satisfied with their sex life (50/72). No statistically significant differences were found between total PISQ scores in women with [mean 35.1 (SD 6.7)] and without [mean 36 (SD 4.9)] mesh complications (p 0.61).

Of the 29 patients with a complication, the complication resolved in 12. A post hoc analysis showed no statistical difference in total PISQ scores in women with a persistent complication or in whom the complication had been resolved.

TABLE 3. Health-Related Quality of Life

	No Complication	With Complication	p- value[‡]
UDI-6 *mean (SD)*	n = 99	n = 29	
Irritative subscale	31.1 ± 28.6	36.1 ± 31.7	0.43
Stress subscale	26.7 ± 26.6	28.8 ± 23.8	0.71
Obstructive subscale	23.6 ± 27.1	29.6 ± 32.1	0.33
IIQ *mean (SD)*			
Physical activity	23.3 ± 23.3	25.5 ± 27.2	0.68
Mobility	26.1 ± 24.6	22.4 ± 24.6	0.49
Social functioning	14.1 ± 18.8	15.6 ±19.1	0.71
Emotional health	18.8 ± 20.2	19.3 ± 23.6	0.92
DDI			
Constipation	13.4 ± 20.6	9.0 ± 15.8	0.31
Painful defecation	9.4 ± 21.6	14.3 ±29.3	0.34
Fecal incontinence	15.0 ± 22.4	13.7 ± 21.3	0.78
Flatus incontinence	27.3 ±29.3	27.2 ±30.7	0.98
PISQ-12 summary score	35.1 ± 6.7	36 ± 4.9	0.61

Not all women answered to all questions.
SD: standard deviation
UDI-6: Urogenital Distress Inventory
IIQ: Incontinence Impact Questionnaire
DDI: Defecatory Distress Inventory
PISQ-12: Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire

Significance cut-off at $p<0.05$

Table 4. Sexual functioning

		No complication (N=54)	With complications (N=18)	P (chi square)
Satisfaction	Very/reasonably satisfied	36 (67)	14 (78)	0.54
	Not satisfied not unsatisfied	10 (19)	1 (6)	
	Fairly/ very dissatisfied	5 (9)	3 (17)	
Urinary incontinence during intercourse	Never	43 (80)	14 (78)	0.48
	Rarely/ sometimes	7 (13)	2 (11)	
	Usually/ always	2 (4)	2 (11)	
Fear of incontinence during intercourse	Never	31 (57)	13 (72)	0.77
	Rarely/ sometimes	15 (28)	4 (22)	
	Usually/ always	7 (13)	1 (6)	
Avoidance	Never	36 (67)	14 (78)	0.20
	Rarely/ sometimes	12 (22)	3 (17)	
	Usually/ always	4 (7)	0	
Negative feelings	Never	28 (52)	10 (56)	0.67
	Rarely/ sometimes	19 (35)	7 (39)	
	Usually/ always	5 (9)	1 (6)	
Aroused	Never	1 (2)	0	0.43
	Rarely/ sometimes	12 (23)	7 (39)	
	Usually/ always	39 (75)	11 (61)	
Orgasm	Never	7 (14)	2 (11)	0.45
	Rarely/ sometimes	18 (35)	3 (17)	
	Usually/ always	27 (52)	13 (72)	
Desire	Never	2 (4)	0	0.37
	Less than once	7 (13)	2 (11)	
	Monthly	17 (32)	10 (56)	
	Weekly/ daily	28 (52)	6 (33)	
Pain	Never	25 (49)	7 (41)	0.65
	Rarely/ sometimes	15 (29)	4 (24)	
	Usually/ always	11 (22)	6 (35)	
Erectile function problems	Never	30 (57)	13 (72)	0.44
	Rarely/ sometimes	22 (42)	5 (28)	
	Usually/ always	1 (2)	0	
Orgasm intensity	Much more intense/ more intense	6 (11)	2 (11)	0.51
	Same	25 (46)	9 (50)	
	Less / much less intense	18 (33)	6 (33)	

* Not all women answered to all questions

Data are expressed as absolute numbers (percentage)

Discussion

This study shows that disease-specific HR-QoL was comparable between women with and without mesh-related complications. Overall domain scores were in the lower range for the UDI-6, IIQ, and DDI, indicating less bother, and in the higher range for the PISQ-12, indicating better sexual functioning. Women with mesh-related complications were more often sexually active as those without, although this difference was not statistically significant.

Apart from our study, only one publication specifically evaluated the relationship between disease-related QoL and the occurrence of mesh-related complications. In the observational study among 114 patients undergoing transvaginal repair with mesh, no significant impact of mesh exposure on the patient's QoL was observed, as with our observation. In addition, mean QoL scores were improved after mesh surgery in both the exposure and non-exposure group.[17] A possible explanation for the similar QoL between women with and without a mesh complication may be that micturition, defecation, and sexual function are mostly related to vaginal anatomy, which is optimized after surgery. The positive impact of restoration of anatomy and elimination of bothersome micturition and defecation symptoms after vaginal mesh surgery counters the negative impact of mesh-related complications.

No statistically significant differences were found in total PISQ scores between women with and without a complication. This is in contrast to the study by Milani et al., who performed an RCT comparing sexual function in women with recurrent POP having either native tissue repair or trocar-guided vaginal mesh surgery. They found that the presence of mesh exposure was independently associated with deterioration of PISQ scores.[18] The probable reason for not observing worsening sexual functioning in women with mesh-related complications is that we used implants with a lower density than Prolift, which was used in the study by Milani et al.[18] It has been shown that lower mesh density is associated with less fibrosis and contraction compared with higher-density mesh.[19]

The sexually active women in our study were relatively satisfied, with the interesting observation that women with a mesh complication, although not statistically significant, appeared to be more satisfied with their sex life. A possible explanation might be that after recovery of a complication, the mere fact of being able to have sexual intercourse again or the absence of pain complaints might be a big relief. Women with a mesh complication were more frequent sexually active. An explanation may be that more sexual activity increases the risk of exposure, as friction is a risk factor for exposure. Future research is needed to investigate whether this observation is a real phenomenon or related to low numbers.

Some design-related issues in this study need to be addressed: Even though health domain scores were in the low range, they were slightly higher in our study compared with other studies that report on QoL in women having a vaginal mesh implant.[4, 20] This might be explained by the difference in duration of follow-up. We report domain scores after a median of 40 months, in contrast with the 12-month follow-up in those studies.[4, 20] We describe vaginal mesh procedures with implants that are no longer marketed. The Elevate® system implanted in most patients in our study was a single-incision technique that provided anterior or posterior repair as well as apical suspension by attachment of the mesh to the sacrospinous ligaments.

We believe results of this study can be extrapolated to other vaginal meshes that are at the market today. Currently available meshes often have similar insertion techniques and are also made of polypropylene, with a similar or even lighter mesh density. This study could be affected by selection bias. Women who consented to participate were of significantly younger age, and younger women may theoretically have better health and therefore may be prone to report a better subjective QoL. Only 58% of our study population reported to be sexually active. We do not know whether refraining from sexual activity was due to a mesh complication; however, this percentage of sexually active women is comparable with previous studies among women with mesh repair and conventional surgery. [4, 20] Comparison of PISQ scores between women with and without a complication showed no difference; however, groups were small.

Several points strengthen our study findings: First, the median follow-up was >3 years, and thus our study represents long-term data. Second, we used disease-specific validated HR-QoL questionnaires to assess subjective outcome measures. Disease-specific questionnaires provide higher face validity and more in-depth assessment of specific issues and concerns to the population under study compared with generic questionnaires, which reliably assess effects of treatment on HR-QoL.[12]

Third, this report is one of few that specifically quantify the effect on sexual functioning in women with mesh-related complications.

In conclusion, this study shows that HR-QoL regarding micturition, defecation, and sexual function is comparable between women with and without a mesh-related complication after vaginal mesh surgery. This is important information in light of the ongoing debate regarding vaginal mesh surgery. The risk of (irreversible) effects of mesh-related complications is the reason many physicians and their patients refrain from vaginal mesh surgery. However, some patients, like women with prolapse recurrence, may benefit from vaginal mesh surgery. Based on this study, women could be informed that there is a risk of complications related to vaginal mesh surgery but that improved QoL related to pelvic floor function is likely to counteract the impact of the mesh-specific complication. This information facilitates a well-balanced treatment selection.

References

1 A. L. Olsen, V. J. Smith, J. O. Bergstrom, J. C. Colling & A. L. Clark. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 1997;89(4):501-6.

2 E. Lowenstein, L. A. Moller, J. Laigaard & H. Gimbel. Reoperation for pelvic organ prolapse: a Danish cohort study with 15-20 years' follow-up. Int Urogynecol J 2018;29(1):119-24.

3 H. Patel, D. R. Ostergard & G. Sternschuss. Polypropylene mesh and the host response. Int Urogynecol J 2012;23(6):669-79.

4 D. Altman, T. Vayrynen, M. E. Engh, S. Axelsen, C. Falconer, et al. Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. N Engl J Med 2011;364(19):1826-36.

5 C. M. Glazener, S. Breeman, A. Elders, C. Hemming, K. G. Cooper, et al. Mesh, graft, or standard repair for women having primary transvaginal anterior or posterior compartment prolapse surgery: two parallel-group, multicentre, randomised, controlled trials (PROSPECT). Lancet 2017;389(10067):381-92.

6 Urogynecologic Surgical Mesh: Update on the safety and effectiveness of transvaginal placement for pelvic organ prolapse. : FDA, 2011.

7 A Randomized controlled trial of anterior colporraphy and Perigee™ as a primary surgical correction of symptomatic cystocele. Annual meeting ICS/IUGA; 2010; Toronto.

8 E. J. Stanford, R. D. Moore, J. P. Roovers, C. Courtieu, J. C. Lukban, et al. Elevate anterior/apical: 12-month data showing safety and efficacy in surgical treatment of pelvic organ prolapse. Female Pelvic Med Reconstr Surg 2013;19(2):79-83.

9 J. C. Lukban, J. P. Roovers, D. M. Vandrie, T. Erickson, S. Zylstra, et al. Single-incision apical and posterior mesh repair: 1-year prospective outcomes. Int Urogynecol J 2012;23(10):1413-9.

10 E. Utomo, I. J. Korfage, M. F. Wildhagen, A. B. Steensma, C. H. Bangma, et al. Validation of the Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) in a Dutch population. Neurourol Urodyn 2015;34(1):24-31.

11 J. S. Uebersax, J. F. Wyman, S. A. Shumaker, D. K. McClish & J. A. Fantl. Short forms to assess life quality and symptom distress for urinary incontinence in women: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program for Women Research Group. Neurourol.Urodyn. 1995;14(2):131-39.

12 S. A. Shumaker, J. F. Wyman, J. S. Uebersax, D. McClish & J. A. Fantl. Health-related quality of life measures for women with urinary incontinence: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program in Women (CPW) Research Group. Qual.Life Res. 1994;3(5):291-306.

13 H. J. van Brummen, H. W. Bruinse, G. van de Pol, A. P. Heintz & C. H. van der Vaart. Defecatory symptoms during and after the first pregnancy: prevalences and associated factors. Int Urogynecol J Pelvic Floor Dysfunct 2006;17(3):224-30.

14 A. G. Groenendijk, E. Birnie, J. P. Roovers & G. J. Bonsel. Contribution of primary pelvic organ prolapse to micturition and defecation symptoms. Obstet Gynecol Int 2012;2012:798035.

15 R. G. Rogers, K. W. Coates, D. Kammerer-Doak, S. Khalsa & C. Qualls. A short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12). Int.Urogynecol.J.Pelvic. Floor.Dysfunct. 2003;14(3):164-68.

16 B. T. Haylen, R. M. Freeman, S. E. Swift, M. Cosson, G. W. Davila, et al. An International Urogynecological Association (IUGA) / International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prostheses (meshes, implants, tapes) & grafts in female pelvic floor surgery. Int Urogynecol J 2011;22(1):3-15.

17 Y. H. Zhang, Y. X. Lu, X. Liu, W. J. Shen & J. X. Liu. [Impact of vaginal mesh exposure on quality of life in patients undergoing transvaginal reconstructive pelvic surgery with polypropylene mesh]. Zhonghua Fu Chan Ke Za Zhi 2012;47(8):608-11.

18 A. L. Milani, M. I. Withagen, H. S. The, I. Nedelcu-van der Wijk & M. E. Vierhout. Sexual function following trocar-guided mesh or vaginal native tissue repair in recurrent prolapse: a randomized controlled trial. J Sex Med 2011;8(10):2944-53.

19 M. Donati, G. Brancato, G. Grosso, G. Li Volti, G. La Camera, et al. Immunological reaction and oxidative stress after light or heavy polypropylene mesh implantation in inguinal hernioplasty: A CONSORT-prospective, randomized, clinical trial. Medicine (Baltimore) 2016;95(24):e3791.

20 M. I. Withagen, A. L. Milani, J. den Boon, H. A. Vervest & M. E. Vierhout. Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse: a randomized controlled trial. Obstet Gynecol 2011;117(2 Pt 1):242-50.

Chapter 4

Efficacy of surgical revision of mesh complications in prolapse and urinary incontinence surgery

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Abstract

Introduction and hypothesis

Women with mesh related complications in prolapse (POP) and stress-urinary incontinence (SUI) surgery may benefit from operative mesh resection to alleviate symptoms. We hypothesized that mesh resection would alleviate symptoms and we aimed to evaluate risks and benefits in these women.

Methods

We carried out a cross-sectional study. Primary outcome was improvement specified as better, unchanged or worsened symptoms after mesh revision surgery. Secondary outcomes were health-related quality of life (Hr-Qol) scores of validated questionnaires, surgical characteristics, and physical findings at follow up visit. Descriptive data were reported with mean and medians. Associations were calculated with Spearman correlation coefficient and Chi square to determine statistical differences between groups.

Results

Fifty-nine women who underwent mesh revision surgery between 2009 and 2016 were included. After a median follow-up of 1.7 (IQR: 1.1–2.4) years, 44 women (75%) reported improvement of symptoms. No significant surgical or patient characteristics were identified that could differentiate which patients did or did not experience cure or complications. A trend was observed to better Hr-Qol scores in women who reported overall improvement after mesh revision surgery. Seventeen (29%) women needed a subsequent operation after mesh removal.

Conclusion

This cross-sectional study shows that mesh revision surgery alleviates symptoms in 75% of women with mesh-related complications. Type of revision surgery and individual characteristics did not seem to matter to the individual chance of cure or complications. These data can facilitate the counselling of women considering mesh revision surgery.

Introduction

Various surgical procedures for POP exist, but the perfect operation combining optimal cure rates and minimal morbidity has yet to be found.

The high failure rates of conventional surgery for POP resulted in the introduction of synthetic vaginal meshes.[1] The rationale of using these meshes is that they trigger fibroblasts to produce new collagen and elastin as part of the foreign body response they induce. Comparative studies have shown that the use of vaginal implants results in improved objective and subjective outcomes, although there are also studies that show no or limited benefit of the use of vaginal implants.[2-5]

Synthetic mesh has also found its place in incontinence surgery. Since the 1990s polypropylene mesh slings have been inserted at the mid-urethral level to treat SUI with good results.[6] However, the use of vaginal implants for POP and SUI can result in specific complications like mesh exposure (mesh protruding in the vagina), erosion (mesh protruding in bladder or bowel), and pelvic pain.

The current literature mainly focuses on incidence and severity of such mesh complications. However, management and improvement of mesh complications have previously been described. These studies report symptom relief and improvement varying between 51%-92%[7-9]

We analyzed the outcomes of mesh re-interventions in our tertiary referral center in order to document risks and benefits and relate outcomes to type of intervention and individual characteristics. This data can facilitate the counselling of women considering mesh revision surgery.

Materials and methods

A cross-sectional study was performed in the Amsterdam University Medical Centers, location AMC in the Netherlands with approval of the Medical Ethics Review Committee.

Population
Patients were eligible for this study if they had a history of mesh revision surgery that had been performed in our tertiary referral hospital between 2009 and 2016. Eligible patients had either a history of a transvaginal mesh (TVM) procedure, an abdominal mesh procedure (sacrocolpo -or sacrohysteropexy; SCP) or mid urethral sling surgery (MUS).

Mesh types
Mesh types that have been excised are: Perigee™, Apogee™, Elevate™, IVS™, Avaulta™, Prolift™, Gynemesh™, Gore-tex™, retropubic and transobturator midurethral slings.

In case of POP, mesh was categorized by the compartment (anterior, apical, posterior) of mesh implantation.

Mesh revision
Mesh revision surgery was done under general or regional anaesthesia. The operations were performed by an alternating team of three urogynaecologists, with two urogynaecologists operating together. We assessed which part or parts of the mesh were most likely causing the problem and needed to be addressed during surgery. We vaginally palpated the body of the mesh, the mesh arms and the connection of the mesh arms to the body. We recorded which parts were painful on examination, and these parts were removed or tension was released. All women received prophylactic antibiotics and had an indwelling urinary catheter during the procedure. In all vaginal approaches, surgery commenced with hydro-dissection of the vaginal wall with adrenaline 1:200 000 combined with xylocaine 2%. The surgical approach depended on the type of mesh complication or mesh type. We classified mesh revision surgery into four types of operations:

1. Removal of a locking eyelet or anchor (this is a polypropylene fixation ring respectively anchor utilized in the Elevate™ mesh kits): the anterior respectively posterior vaginal wall is incised, dependent on the type of mesh placed at the index surgery. After incision of the vaginal wall, the locking eyelet or anchor is identified, dissected and removed.

2. Exposure correction: the epithelium around the exposure is circumcised and mobilized. The vaginal epithelium surrounding the exposure is discarded. The exposed mesh is excised, and the vaginal epithelium surrounding the removed part of the mesh is mobilized and approximated by absorbable sutures.

3. Mesh resection/cleaving: Vaginal approach: the vaginal wall is incised and after identification of the mesh, it is dissected by keeping close proximity to the mesh, thereby preventing bladder damage or bowel injury. Tension on the mesh is released by cutting the mesh followed by resection, including the major part of the mesh arms. Abdominal approach: this can be the preferable route, by either laparoscopy or laparotomy, when removing mesh of SCP. It can be combined with a vaginal approach. The mesh is identified by careful dissection of the surrounding tissue and either completely removed or cut to release tension.

4. Removal of mesh from the bladder: this is performed by laparotomy and subsequent open cystotomy and excision of the exposed mesh from the bladder. After resection of the mesh the bladder mucosa is carefully examined to make sure that all mesh protruding from the bladder wall has been removed. If complete mesh resection from the bladder cannot be accomplished by cystotomy alone, the procedure is combined with a vaginal approach to achieve complete resection of the mesh erosion.

Study procedures

Eligible patients received a letter regarding the study and could opt out if they did not want to be contacted. The patients that did not opt out were contacted by phone and asked to participate. Participants were asked to visit the study site. A gynaecological examination was performed by an urogynaecologist to assess POP by means of Pelvic Organ Prolapse Quantification (POP-Q). This examination was used to assess for POP recurrence. Recurrence was defined as stage 2 or more pelvic organ prolapse according to the POP-Q scoring system. Data that could not be provided by the patient were abstracted from the medical records.

Outcome measures

The primary outcome measure was perceived improvement after mesh revision surgery. This outcome was scored by asking patients to indicate whether they experienced improvement, no change or aggravation of their symptoms after revision surgery.

Subjective cure was assessed by the Patient Global Impression of Change (PGI-C).[10] The PGI-C reports on outcome concerning, activity, symptoms, emotions and general quality of life, related to the patients mesh complaints. Patients could select an answer on a 7-point Likert scale: “no change or worsening,” “almost no change,” “a little bit of improvement, but no notifiable change,” “a little bit of improvement, but no significant change,” “a little bit of improvement and a notifiable change,” better and a worthwhile change” and “very much better, a substantial change.” They were defined as cured when their answers to the PGI-C were “better” or “very much better.”

All patients were asked to complete the Urogenital Distress Inventory (UDI-6), the Incontinence Impact Questionnaire (IIQ-7), the Defecatory Distress Inventory (DDI) and the Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-12).[11-15]

Serious adverse events (SAE) were categorized in per- and postoperative complications that required re-admittance to the hospital or repeat surgery.

Statistical analysis

Data were analyzed using IBM SPSS Statistics 25.

Descriptive statistics were done as appropriate. For categorical data and not normally distributed numerical data, median and interquartile range (IQR) was reported. For continuous data mean with standard deviation was reported. For frequencies, number plus percentage was given. Differences between groups were tested with independent t-tests for normally distributed data. In some cases only the year of mesh insertion was registered. In these cases, the mesh insertion date has been set on the first of January of that specific year to calculate the follow-up period.

Subjective improvement was scored in relation to the type of mesh revision operation that had been performed.

Scores to disease-specific questionnaires (UDI-6, IIQ-7, DDI, PISQ,) were calculated appropriately.[16] Hr-QoI scores were calculated and reported as an overall score and separately for women that experienced improvement, had experienced no change or had aggravation of symptoms after mesh revision surgery. Differences between these 3 groups were calculated with Kruskal Wallis test for multiple comparisons of not normally distributed numerical data.

A chi-square test was done to assess statistical difference between the change in symptoms and the type of operation and to assess whether SAEs differed between types of surgery.

Results

Between 2009 and 2016, 92 patients had mesh revision surgery in our University hospital. Fifty-nine patients (64%) were included in this study. The women that were not included could not be reached or refused participation. The current status of their complaints were obtained by either chart review or by telephone answers. This is shown in Fig. 1. Baseline characteristics are shown in table 1. Nineteen women (32%) had persisting complaints after previous mesh removal surgery, before they were referred to our center. The most important complaint and reason for opting for mesh revision surgery was pain (including dyspareunia). This was reported by 46 (78%) women.

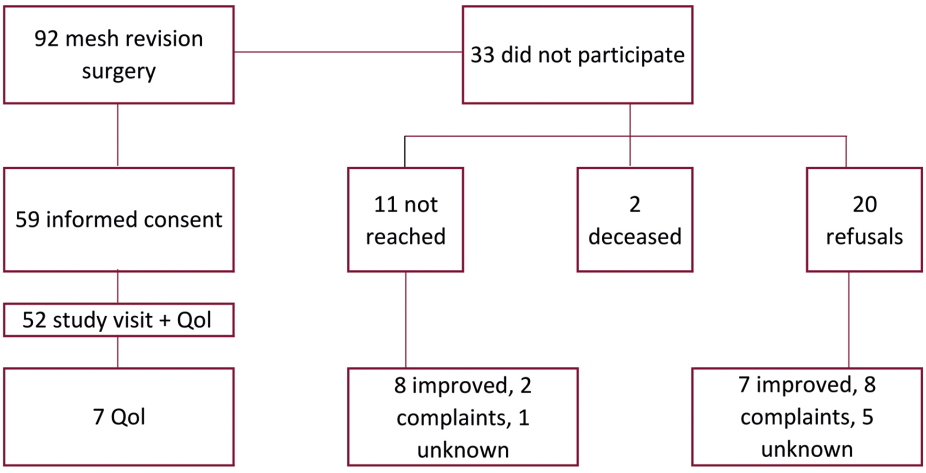

Figure 1. Flow chart of patients included in the study

TABLE 1. Baseline Characteristics

Patient demographics	Missing	n = 59
Age (years) *median (IQR)**		62 (54-67)
Follow up (years) mesh insertion – intervention¥ *median (IQR)*	1	4.2 (1.2-6.9)
Time since mesh placement >1 year *n(%)*	1	45 (77.6)
Follow up (years) intervention- follow up visit¶ *median (IQR)*		1.7 (1.1-2.4)
Postmenopausal *n, (%)*	12	36 (76.6)
BMI		25.7 (23.4-28.7)
Parity *median (IQR)*	1	2 (2-3)
Vaginal delivery *n(%)*	1	58 (98.3)
Caesarean Section *n(%)*	1	4 (6.8)
Forceps/ ventouse *n(%)*	9	16 (27.2)
Smoking *n (%)*		3 (5.1)
History of prolapse surgery		
Type of mesh n *(%)*		
Vaginal mesh implant		48 (80)
Midurethral sling (MUS)		6 (10)
Sacro- colpo/ hysteropexia		6 (10)
Type of second mesh n *(%)*		
Vaginal mesh implant		8 (13)
Midurethral sling (MUS)		1 (1.6)
Sacro- colpo/ hysteropexia		2 (3.3)

TABLE 1. Baseline Characteristics *(continued)*

Patient demographics	Missing	n = 59
Type of third mesh n *(%)*		
Vaginal mesh implant		1 (1.6)
Midurethral sling (MUS)		0
Sacro- colpo/ hysteropexia		1 (1.6)
Previous mesh revision surgery		19 (32)

*IQR: interquartile range

¥ Time elapsed between the primary mesh insertion and the mesh revision under study

¶ Time elapsed between de mesh revision under study and the follow up visit

Chart review showed that fibrosis and too much tension of the mesh was the most frequent finding on physical examination and was observed in 36 (61%) women. Exposure was seen in 18 (31%) women. In three of these women both too much tension as well as an exposure was found.

Improvement was reported by 44 women (75%), 7 (13%) did not experience any change and 3 (5%) experienced deterioration of their symptoms. In five subjects the outcome was missing. Subjective cure measured with the PGI-C was reported by 28 (47%) women (outcome missing in 4 patients). When comparing outcome per type of mesh revision surgery (MUS, abdominal mesh or vaginal mesh) there was no statistical difference in improvement or PGI-C scores between the various mesh categories.

Outcome per mesh type is shown in Table 2. Six women had a total mesh resection; in 39 women the mesh was partially resected. There was no significant difference in improvement between total and partial mesh resection (p=0.52) or in serious adverse event (p=0.94).

TABLE 2. Outcome categorized per mesh type.

	N	Improved (n/%)	Similar (n/%)	Worsened (n/%)	p-value	PGI-C (cure) (n/%)	p-value
Vaginal mesh	47	34 (72)	7 (15)	4 (9)		22 (47)	
Abdominal mesh	6	5 (83)	0	1 (17)		4 (67)	
MUS	6	4 (67)	0	1 (17)		2 (33)	
Overall	59	44 (75)	7 (13)	3 (5)	0.41	28 (47)	0.38

The type of revision surgery as classified in the methods section did not show a statistical difference in the change in symptoms (p=0.49).

The occurrence of a SAE was not related to the type of intervention (p=0.74) or mesh type (MUS, vaginal or abdominal mesh) (p=0.59).

No correlation was found between effects on symptoms after revision surgery and BMI, menopause, smoking, and type of mesh graft, time between mesh insertion and moment of mesh revision, sexual activity and number of reoperations.

All vaginal mesh implants were removed vaginally. In one case, an erosion of a retropubic midurethral sling has been removed abdominally, since it had eroded into the bladder. In four cases the approach has been abdominal and vaginally combined (twice by laparoscopy) and in one patient by abdominal approach only. These cases all concerned complications of an abdominal mesh.

In 41 (70%) women no concomitant vaginal surgery was performed during the mesh revision surgery; in 10 a native tissue repair and in 6 a MUS was executed simultaneously. In two women, a mesh revision was combined with a vaginal mesh insertion. In one woman, a mesh was inserted in the same compartment as the revision. In the other, the mesh was inserted in a different compartment. There was no correlation regarding change of mesh-related symptoms and concomitant surgery (p=0.82).

The surgical characteristics are shown in Table 3. SAEs were reported in eight patients. In one patient, a bowel lesion occurred during abdominal mesh resection and a jejunostomy had to be performed to manage the complication. In the vaginal mesh group, seven women had complications. Two women were registered as having a bladder lesion; in one of these women there was a minor suspicion of this lesion. One woman had a minor lesion of the serosa of the bowel. One woman had excessive bleeding during dissection of the anterior wall that was performed to insert an anterior mesh; during this operation the management of an exposure of a previous mesh did not cause the bleeding.

TABLE 3. Surgical characteristics of the study population

	Missing	n =59
Mesh categories revised	1	
Single incision		15 (26.3)
Multiple incision		20 (35.1)
Mesh in more compartments		11 (18.6)
Sacrocolpopexia		6 (10.2)
MUS		6 (10.2)
Mesh revisions performed		
Exposure		7 (11.9)
Locking eyelet/ anchor		5 (8.5)
Mesh resection		45 (76.3)

TABLE 3. Surgical characteristics of the study population *(continued)*

Mesh categories revised	Missing 1	n =59
Mesh resection from bladder		2 (3.4)
Time in surgery* (minutes)	10	57 (36-103)
Blood loss* (ml)	7	17.5 (0-50)
(Serious) adverse events		8 (13.3)
Per- operative complications		5 (8.3)
Blood loss >500ml		1 (1.6)
Bladder lesion¥		2 (3.3)
Bowel lesion		2 (3.3)
Post-operative complications requiring re-admittance/ surgery		3 (5.0)
Hematoma (hospital admittance)		1 (1.6)
Post-operative bleeding (repeat surgery)		2 (3.3)

Data are expressed as 1.median (* IQR= interquartile range) or 2. absolute numbers (percentage)
¥ In 1 patient there was a minor suspicion of a bladder lesion and an indwelling catheter was left in situ for 5 days

In 14 (24%) women, 23 reoperations were performed after the mesh revision surgery in our tertiary center. Indications for these reoperations were persistent mesh complications, POP surgery, SUI surgery or complication management. Some women needed a combination of procedures; therefore, the number of reoperations is higher than the number of patients. Ten women had a reoperation because of persisting mesh complications; one woman needed two re-operations. Five women had subsequent POP surgery, and a MUS was placed in four women. Two women had a reoperation because of postoperative haemorrhage. At the follow-up visit, ten women were scheduled for a subsequent operation because of persisting mesh complications (n = 7), prolapse recurrence (n = 1) or urinary incontinence (n = 2). Of these ten women, seven already had a prior reoperation after the index mesh removal.

Overall POP recurrence in any compartment was seen in 18 women (31%; outcome missing in 12); these were mostly anterior and posterior compartment prolapses. Anterior compartment prolapse after anterior mesh revision occurred in five (8%) women. Two women who underwent an apical compartment mesh resection encountered prolapse recurrence of the apical compartment. Two woman had a posterior compartment recurrence after posterior mesh revision. None of the women had a prolapse POPQ stage 3 or 4. More than half of the women that had MUS revision surgery reported no to mild SUI symptoms. Table 4 shows the Hr-QoI-scores of women that reported improvement, no change and worsened symptoms after mesh revision surgery. Women reporting improvement had better mean UDI-6 and IIQ-7 scores (not statistically significant).

TABLE 4. Health-related quality of life

	n	Improved	n	Similar	n	Worsened	n	p- value†
UDI-6 ˜ *mean (SD*)*	46	34.5 ± 19.5	37	44.4 ± 25.3	6	66.7 ± 22.2	3	0.07
Irritative subscale	49	39.6 ± 22.9	40	41.7 ± 25.3	6	66.7 ± 33.3	3	0.34
Stress subscale	50	24.4 ± 21.1	41	41.7 ± 41.8	6	61.1 ± 34.7	3	0.10
Obstructive subscale	48	40.6 ± 28.3	39	50.0 ± 21.1	6	72.2 ± 9.6	3	0.10
IIQ-7‡ *mean (SD*)*	45	15.8 ± 20.2	38	22.5 ± 22.0	5	56.3 ± 14.7	2	0.09
Physical activity	47	20.8 ± 24.4	40	20.0 ± 29.8	5	66.7 ± 23.6	2	0.11
Mobility	48	17.1 ± 21.2	40	36.1 ± 37.1	6	58.3 ± 11.8	2	0.04
Social functioning	47	12.8 ± 19.7	39	33.3 ± 36.5	6	50.0 ± 23.6	2	0.04
Emotional health	47	17.1 ± 26.9	39	33.3 ± 31.6	6	50. ± 0.00	2	0.09
DDI** *mean (SD*)*	41	15.5 ± 13.9	36	6.1 ± 6.1	3	18.2 ± 17.1	2	0.41
Constipation	43	16.2 ± 22.0	37	5.6 ± 9.6	3	11.1 ± 19.2	3	0.65
Painful defecation	45	18.4 ± 26.2	39	11.1 ± 19.2	3	16.7 ± 28.9	3	0.92
Fecal incontinence	47	5.3 ± 10.8	41	5.6 ± 9.6	3	11.1 ± 19.2	3	0.80
Flatus incontinence	47	25.2 ± 28.6	41	11.1 ± 19.2	3	22.2 ± 38.5	3	0.70
PISQ-12 ¥ summary score	25	32.3 ± 3.6	23	30.5 ± 6.4	2		0	0.62

* SD: standard deviation

˜ UDI-6: Urogenital Distress Inventory

‡ IIQ: Incontinence Impact Questionnaire

**DDI: Defecatory Distress Inventory

¥ PISQ-12: Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire

† Significance cut-off at $p<0.05$

Not all women answered all questions.

Discussion

This cross-sectional study demonstrates that 75% of women undergoing mesh revision surgery because of mesh-related complications after POP or SUI surgery experienced an improvement of symptoms, while in 5% symptoms worsened. Subjective cure measured with the PGI-C was reported by 47% of patients. There was no statistical difference in outcome among the MUS, abdominal and vaginal mesh resections. Twenty-nine percent of women were indicated to need an additional operation because of persistent mesh complications, POP recurrence or SUI.

Improvement of symptoms or the occurrence of SAEs was not related to the type of intervention performed as classified in the Methods section. This outcome was scored after a median follow-up of 1.7 (IQ range: 1.1–2.4) years after revision surgery.

The percentage of symptom relief is consistent with other studies. Reports of symptom relief vary between 46%- 92% with the difference that these other reports have considerable shorter follow up than our study [8, 17, 18] except for the study of Warembourg et al., which report a cure rate of 78% with a mean follow-up of 41 months (95%CI: 34.3 -47.7).[9]

The main reason for having mesh revision surgery in our population was pain (including) dyspareunia, which was reported by 78% of patients. Pain being the main indication for revision surgery has also been reported by other researchers [17, 19]. Unfortunately, pelvic and vaginal pain is difficult to treat. The causal factor of pain after mesh surgery remains unclear, but it has been hypothesized that too much tension on the mesh, fibrosis and exposure are factors that contribute to pain symptoms.

In the majority of women in our study (61%) fibrosis or too much tension on the mesh assessed by palpation was found at pelvic examination prior to revision surgery.

When women present to our clinic, with pain complaints after a mesh insertion, we examine them and try to objectify whether their complaints are due to hypertonia of the pelvic floor muscles or because of a mesh complication. In case of the first, we refer women for pelvic floor physical therapy, but when the mesh itself seems to cause the problem, we proceed to surgical resection. In some women, additional pelvic floor physical therapy is needed after surgery.

Our surgical approach to the treatment of mesh complications is to release the tension and remove the most painful part of the mesh.

How much of the mesh needs to be removed when pain complaints are the indication for revision surgery depends on the severity of symptoms, location of tension/ fibrosis and the risk of complications due to proximity of the mesh to the bladder or rectum.

Consequently, in some patients as much mesh as possible was removed, but in most patients mesh remnants were left in situ.

There was no statistical difference in change of symptoms between the four surgical approaches that we exercise in our hospital or category of mesh (MUS, abdominal mesh, vaginal mesh) that was removed, or in improvement between total and partial mesh removal. It seems that resection of as much mesh as possible is not mandatory to achieve symptom relief. Wolff et al. also concluded in their review that total mesh removal is not always more beneficial to the patients in comparison to partial mesh resection.[20]
This is important information to share with the patient, since some patients believe that only complete removal of the mesh will result in resolution of their symptoms.

When informing women about mesh revision surgery, the chance of having prolapse recurrence should be subject of the counselling. Ideally, surgery should alleviate mesh-related complaints, without causing new prolapse-related problems. In this study, we showed that the chance of prolapse recurrence in the specific compartment where the mesh had been removed was most common in the anterior compartment (8%). This anterior recurrence was less prevalent than in the study of Marcus Braun that reported 19% cystocele recurrence after removal of the vesico-vaginal mesh.[21] This might be explained by the fact that Marcus Braun et al. saw most recurrences after complete mesh resection, whereas most patients in our study underwent a partial resection.

In MUS revisions, there is a risk of relapse of SUI symptoms. In our population, 33% had SUI at follow up visit, but one must take into account that tape revision was only performed in six patients when interpreting this outcome. Other studies describe that 14-23% of women have surgery for recurrent SUI after tape revision and 49% have SUI recurrence.[22-24]

Hr-Qol was assessed at follow-up visit in the current study. The UDI-6 and IIQ-7 scores were better in the women who reported improvement after revision, although this outcome did not reach statistical significance except for the subdomains of mobility and social functioning of the IIQ-7. However, one should consider that the sample sizes were small.

This study has some limitations that need to be addressed. Not all women that had mesh revision surgery in our tertiary center consented to participate in the study, and some women only consented to fill out the Hr-Qol questionnaires. The results can be affected by selection bias.

In this study, various types of mesh have been revised. The outcome could differ depending on the type of mesh that has been revised, but on the contrary this study is strengthened by the fact that it gives a representation of the daily practice in a tertiary

center. Our center has a special interest in mesh-related complications and has developed much experience in the treatment of these problems. These facts have to be kept in mind when interpreting the current data. The outcome of this study may not be generalizable to other settings. Another strength of this study is that it reports on subjective outcomes after revision surgery, including the outcome of standardized questionnaires concerning Hr-QoI after a long-term follow-up.

Conclusion

This cross-sectional study shows that mesh revision surgery alleviates symptoms in 75% of women who had mesh-related complications after POP and/or SUI surgery. The type of revision surgery and individual characteristics did not seem to matter to the individual chance of cure or complications. Seventeen (29%) women needed a subsequent operation after mesh removal. These data can facilitate the counselling of women considering mesh revision surgery.

References:

1 P. Debodinance, J. Berrocal, H. Clave, M. Cosson, O. Garbin, et al. *[Changing attitudes on the surgical treatment of urogenital prolapse: birth of the tension-free vaginal mesh]*. J Gynecol Obstet Biol Reprod (Paris) 2004;33(7):577-88.

2 D. Altman, T. Vayrynen, M. E. Engh, S. Axelsen, C. Falconer, et al. *Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse*. N Engl J Med 2011;364(19):1826-36.

3 C. M. Glazener, S. Breeman, A. Elders, C. Hemming, K. G. Cooper, et al. *Mesh, graft, or standard repair for women having primary transvaginal anterior or posterior compartment prolapse surgery: two parallel-group, multicentre, randomised, controlled trials (PROSPECT)*. Lancet 2017;389(10067):381-92.

4 M. I. Withagen, A. L. Milani, J. den Boon, H. A. Vervest & M. E. Vierhout. *Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse: a randomized controlled trial*. Obstet Gynecol 2011;117(2 Pt 1):242-50.

5 C. Maher, B. Feiner, K. Baessler, C. Christmann-Schmid, N. Haya, et al. *Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse*. Cochrane Database Syst Rev 2016;2:CD012079.

6 U. Ulmsten, L. Henriksson, P. Johnson & G. Varhos. *An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence*. Int Urogynecol J Pelvic Floor Dysfunct 1996;7(2):81-5; discussion 85-6.

7 E. C. Crosby, M. Abernethy, M. B. Berger, J. O. DeLancey, D. E. Fenner, et al. *Symptom resolution after operative management of complications from transvaginal mesh*. Obstet Gynecol 2014;123(1):134-9.

8 M. M. Tijdink, M. E. Vierhout, J. P. Heesakkers & M. I. Withagen. *Surgical management of mesh-related complications after prior pelvic floor reconstructive surgery with mesh*. Int Urogynecol J 2011;22(11):1395-404.

9 S. Warembourg, M. Labaki, R. de Tayrac, P. Costa & B. Fatton. Reoperations for mesh-related complications after pelvic organ prolapse repair: 8-year experience at a tertiary referral center. Int Urogynecol J 2017;28(8):1139-51.

10 H. Hurst & J. Bolton. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther 2004;27(1):26-35.

11 E. Utomo, I. J. Korfage, M. F. Wildhagen, A. B. Steensma, C. H. Bangma, et al. Validation of the Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) in a Dutch population. Neurourol Urodyn 2015;34(1):24-31.

12 J. S. Uebersax, J. F. Wyman, S. A. Shumaker, D. K. McClish & J. A. Fantl. Short forms to assess life quality and symptom distress for urinary incontinence in women: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program for Women Research Group. Neurourol Urodyn 1995;14(2):131-9.

13 H. J. van Brummen, H. W. Bruinse, G. van de Pol, A. P. Heintz & C. H. van der Vaart. Defecatory symptoms during and after the first pregnancy: prevalences and associated factors. Int Urogynecol J Pelvic Floor Dysfunct 2006;17(3):224-30.

14 A. G. Groenendijk, E. Birnie, J. P. Roovers & G. J. Bonsel. Contribution of primary pelvic organ prolapse to micturition and defecation symptoms. Obstet Gynecol Int 2012;2012:798035.

15 R. G. Rogers, K. W. Coates, D. Kammerer-Doak, S. Khalsa & C. Qualls. A short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12). Int.Urogynecol.J.Pelvic. Floor.Dysfunct. 2003;14(3):164-68.

16 C. R. Kowalik, M. M. E. Lakeman, A. T. de Kraker & J. Roovers. Effects of mesh-related complications in vaginal surgery on quality of life. Int Urogynecol J 2018

17 C. E. Skala, K. Renezeder, S. Albrich, A. Puhl, R. M. Laterza, et al. Mesh complications following prolapse surgery: management and outcome. Eur J Obstet Gynecol Reprod Biol 2011;159(2):453-6.

18 B. Ridgeway, M. D. Walters, M. F. Paraiso, M. D. Barber, S. E. McAchran, et al. Early experience with mesh excision for adverse outcomes after transvaginal mesh placement using prolapse kits. Am J Obstet Gynecol 2008;199(6):703 e1-7.

19 S. Abbott, C. A. Unger, J. M. Evans, K. Jallad, K. Mishra, et al. Evaluation and management of complications from synthetic mesh after pelvic reconstructive surgery: a multicenter study. Am J Obstet Gynecol 2014;210(2):163 e1-8.

20 G. F. Wolff, J. C. Winters & R. M. Krlin. Mesh Excision: Is Total Mesh Excision Necessary? Curr Urol Rep 2016;17(4):34.

21 N. Marcus-Braun & P. von Theobald. Mesh removal following transvaginal mesh placement: a case series of 104 operations. Int Urogynecol J 2010;21(4):423-30.

22 G. Agnew, P. L. Dwyer, A. Rosamilia, G. Edwards & J. K. Lee. Functional outcomes for surgical revision of synthetic slings performed for voiding dysfunction: a retrospective study. Eur J Obstet Gynecol Reprod Biol 2012;163(1):113-6.

23 N. F. Davis, L. G. Smyth, S. K. Giri & H. D. Flood. Evaluation of endoscopic laser excision of polypropylene mesh/sutures following anti-incontinence procedures. J Urol 2012;188(5):1828-32.

24 N. Abraham, I. Makovey, A. King, H. B. Goldman & S. Vasavada. The effect of time to release of an obstructing synthetic mid-urethral sling on repeat surgery for stress urinary incontinence. Neurourol Urodyn 2017;36(2):349-53.

Chapter 5

Are polypropylene mesh implants associated with systemic autoimmune inflammatory syndromes? A systematic review

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Abstract

Purpose

The surgical implantation of polypropylene (PP) meshes has been linked to the occurrence of systemic autoimmune disorders. We performed a systematic review to determine whether PP implants for inguinal, ventral hernia or pelvic floor surgery are associated with the development of systemic autoimmune syndromes.

Methods

We searched Embase, Medline, Web of Science, Scopus, Cochrane library, clinicaltrialsregister.eu, clinicaltrails.gov and WHO-ICTR platform. Last search was performed on November 24th 2021. All types of studies reporting systemic inflammatory/autoimmune response in patients having a PP implant for either pelvic floor surgery, ventral or inguinal hernia repair were included. Animal studies, case reports and articles without full-text were excluded. We intended to perform a meta-analysis. The quality of evidence was assessed with the Newcastle-Ottawa Scale. This study was registered at Prospero (CRD42020220705).

Results

Of 2137 records identified, 4 were eligible. Two retrospective matched cohort studies focused on mesh surgery for vaginal prolapse or inguinal hernia compared to hysterectomy and colonoscopy, respectively. One cohort study compared the incidence of systemic conditions in women having urinary incontinence surgery with and without mesh. These reports had a low risk of bias. A meta-analysis showed no association when comparing systemic disease between mesh and control groups. Calculated Risk Ratio was 0.9 (95% CI 0.82-0.98). The fourth study was a case-series with a high risk of bias, with a sample of 714 patients with systemic disease, 40 of them had PP mesh implanted.

Conclusion

There is no evidence to suggest a causal relationship between being implanted with a PP mesh and the occurrence of autoimmune disorders.

Introduction

In patients with pelvic organ prolapse (POP) or inguinal hernia, surgical outcome with native tissue has a high risk of recurrence. The introduction of polypropylene (PP) implants to surgically repair connective tissue defects has resulted in improved surgical outcome.[1, 2] These implants have been used since the 1960s for inguinal- and ventral hernia repair and since the 90s for stress-urinary incontinence (SUI) and POP repair.[3-6] Although PP implants have been proven to decrease the recurrence risk, the risk of mesh-related complications has to be weighed against the benefits.

Well-known mesh-related complications include nerve entrapment, mesh erosion, mesh exposure and pain.[7, 8] Whether the occurrence of systemic inflammatory symptoms can also be considered a mesh-related complication is still under debate. It has been postulated that PP can cause a systemic autoimmune inflammatory disorder, as has been described in women with silicone breast implants, called autoimmune/inflammatory syndrome induced by adjuvants (ASIA).[9] The rationale behind this hypothesis is that the local inflammatory reaction after mesh insertion, might result in a systemic up-regulation of inflammatory mediators.[10] If PP would prove to be an adjuvant for the development of systematic inflammatory response symptoms, this would have huge implications for the treatment of patients with symptoms of systemic immune disease, as it would imply that only a complete mesh removal could result in symptom reduction. Such surgery is invasive, can be technically challenging and would therefore only be acceptable if the indication is indisputable.

The objective of this systematic review is to study if there is an association with PP implants for inguinal and ventral hernia repair or pelvic floor surgery and the development of systemic autoimmune syndromes. All types of studies reporting the outcome of developing systemic autoimmune syndrome(s) in patients having a PP mesh implant for SUI, POP, ventral or inguinal hernia were systematically reviewed.

Materials and Methods

This review was conducted according to PRISMA guidelines.[11] The protocol was previously registered and published in Prospero (https://www.crd.york.ac.uk/prospero; Registration number: CRD42020220705). A narrative review in Dutch describing the systemic effect of PP implants in Urogynecology has been published previously.[12]

Eligibility criteria
The study was set up according to the PICO framework for the domain of harm.

Inclusion criteria were experimental, prospective, cross-sectional and observational studies (case-control studies, cohort studies, case-series) reporting evolvement of systematic inflammatory or autoimmune diseases after PP implantation. We required full journal publication, with the exception of online clinical trial results, summaries of otherwise unpublished clinical trials and abstracts with sufficient data for analysis.

Studies describing PP implants not intended for POP, SUI, ventral hernia or inguinal hernia were excluded. Other exclusion criteria were case-reports and articles describing data obtained from animal studies. Neither language restriction nor time limitations were imposed.

Patients >18 years of age and having a PP mesh implant for either POP, SUI, ventral hernia or inguinal hernia were considered. The outcome was a systemic inflammatory or autoimmune response.

Search strategy

A systematic search strategy was developed to identify published studies on Embase (Ovid SP platform), Medline (Ovid SP platform), Web of Science, Scopus and Cochrane library. Furthermore, clinicaltrialsregister.eu, clinicaltrails.gov and WHO-ICTR platform were searched to include unpublished trial reports. Lastly, upon final inclusion of relevant studies a snowball method (forward and backward reference checking) was performed on Google Scholar and Microsoft Academics to avoid missing relevant papers.

The searches were performed and concluded on November 24th 2021. Subsequently, forward and backward searches were performed on November 24th 2021. Three different search blocks containing a combination of Mesh/Emtree and free text combinations, were applied as followed (full search strategy can be found in Appendix A):

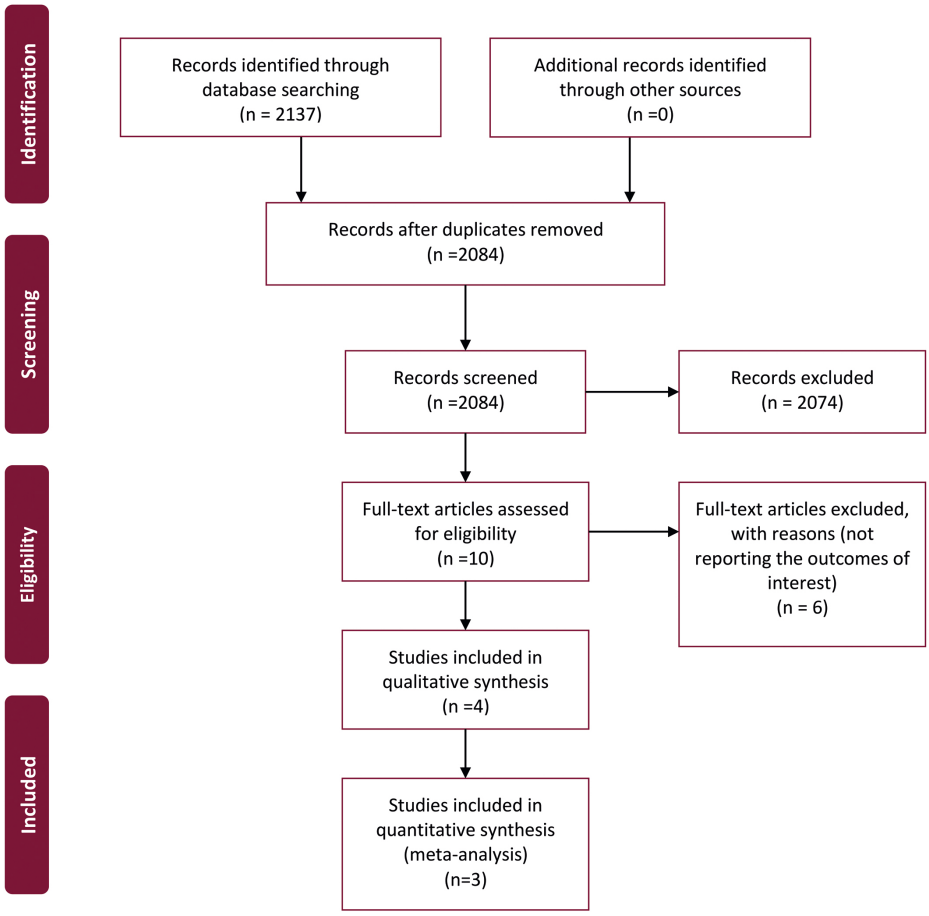
1) (pelvic organ prolapse or uterine prolapse or Hernia, Ventral or Hernia, Inguinal or Urinary Incontinence, Stress or Cystocele or Hernia, Abdominal or Rectocele or Herniorrhaphy)
   AND
2) (Polypropylenes or Surgical Mesh)
   AND
3) (autoimmunity or autoimmune diseases or systemic inflammatory response syndrome or Inflammation or Foreign-Body Reaction)

Selection of articles

Two reviewers (SZ, CK) independently did the screening and selection of the studies. Before starting the selection of articles, the reviewers had a meeting to discuss the eligibility criteria. For selecting eligible studies, Rayyan QCRI (https://rayyan.qcri.org) was used.[13]

Both reviewers screened all articles, first titles, then abstracts and lastly full texts. A flowchart of study selection according to the PRISMA statement provides insight into the screening process (See Fig. 1).

Figure 1. Flow chart of study inclusion.



Data extraction (selection and coding)

Data extraction was done by CK using a predefined form, that included author, country, year of publication, journal, publication type, aim, study type, source of patients, primary outcome, follow-up time, mean age, number of patients included, gender, eligibility criteria and results. Subsequently, a second reviewer (SZ) checked extracted data.

Risk of bias (quality) assessment
Risk of bias was assessed using the Newcastle-Ottawa Scale at study level.[14] For each included study, the appropriate design scale was used. Two reviewers (SZ, WZ) independently assessed the risk of bias of the included studies using this validated tool. A description of risk of bias was done, as suggested by the scale developers. The quality of each study, including selective reporting within a study, will be weighted in the conclusion of this review.

Strategy for data synthesis
Data has been summarized narratively by outcomes that were described in the particular study articles. If more than one comparative study was found, a meta-analysis was performed and I^2 presented.

Analysis of subgroups or subsets
Further subgroup analyses will be performed if appropriate.

Results

A total of four studies have been included in this review. The search of Embase (Ovid SP platform), Medline (Ovid SP platform), Web of Science, Scopus and Cochrane library and clinicaltrialsregister.eu, clinicaltrails.gov and WHO-ICTR platform provided 2137 citations. After removing duplicates, 2084 records have been screened. Screening on title and abstract resulted in ten full text articles that were assessed for eligibility. Six of these did not meet the inclusion criteria. Finally, four studies were included in the present review (see Fig. 1).

Critical appraisal
To determine the quality of the included studies, the Newcastle Ottawa Scale was used. For both studies of Chughtai [15, 16], the risk of bias is low: the selection of patients was considered representative, the cohort selection was done appropriately, surgical records seemed appropriate for selecting patients and outcomes were not present at start of the study. Comparability of cohorts was assessed. The outcomes were derived through record linkage, which imposes medium risk of bias. Follow-up for both the exposed cohort as well as controls was two years and considered appropriate.

The risk of bias for the study of Muller [17] was considered low since a large number of patients was selected from a cohort of women who underwent SUI surgery with (intervention) or without (controls) mesh. The minimal follow-up duration of 5 year should be adequate and the study corrected for significant confounding factors including age, ethnicity and pre-existing comorbidities. The study of Cohen Tervaert [9], has low risk of bias considering the selection of patients with autoimmune disease, but patients were

selected from a cohort with known autoimmune symptoms and therefore the outcome was present at start of the study. A non-exposed cohort was lacking. There was no description of ascertainment of exposure. Comparability of cohorts based on neither design nor analysis was described. Outcome assessment was done by record linkage. Follow-up was not performed (see Table 1).

Table 1. Risk of bias

		Chugthai Hernia	Chughtai AJOG	Muller	Tervaert
Selection	Representative				
	Controls				
	Exposure ascertainty				
	Outcome not present at start study				
Comparability	Are cohorts comparable				
Outcome	Assessment validity				
	Adequate follow-up				
	Adequate follow-up cohorts				

RISK OF BIAS

LOW
MEDIUM
HIGH
UNCLEAR

Study characteristics

Two of the selected studies were retrospective cohort studies with matched controls and were performed in the USA, by Chughtai et al.[15, 16] One study was a national cohort study that has been carried out in the United Kingdom by Muller et al. [17]

Cohen Tervaert performed the fourth study in the Netherlands, Canada and Belgium. This was a case series.[9] The summary of included studies is shown in Table 2.

The studies have been conducted between 2008 and 2019. When combining the three cohort studies eligible for meta-analysis, a total of 104,594 matched participants had PP implants, because of inguinal hernia repair, mesh for POP or SUI. These participants were matched with 33,253 controls.

The control groups in the studies of Chughtai et al. [15, 16] were extracted from a cohort of colonoscopy patients and a second cohort of patients with a history of vaginal hysterectomy. All subjects in the cohort studies were individually matched by patient characteristics and comorbidities. The women included in the study of Muller et al. [17] were all women that had SUI surgery either with or without mesh. Patient characteristics, demographic data and co-morbidities were comparable.

The study of Cohen Tervaert [9], being a case series, contained a sample of 714 participants, of which 40 had a PP mesh implant.

The primary outcome of the studies by Chughtai et al.[15, 16], was the development of systemic autoimmune disorders (SAID) at the entire follow-up period. The average follow-up period of both studies by Chughtai et al, was 6 years. SAID was defined in one study as an enumeration of various autoimmune disorders (Grave's disease, Hashimoto's thyroiditis, pernicious anaemia, autoimmune haemolytic anaemia, autoimmune thrombocytopenic purpura, amyotrophic lateral sclerosis, multiple sclerosis, Guillain–Barré Syndrome, myasthenia gravis, Goodpasture syndrome, vasculitis, celiac disease, pemphigus vulgaris, systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome, dermatomyositis, polymyositis, rheumatoid arthritis, ankylosing spondylitis and fibromyalgia).[16] Secondary outcomes included development of SAID at 6 months, 1 year and 2 year follow-up time point.

The main outcome measure of the study of Muller et al. [17] was the first post-operative admission with a record of at least one of 29 autoimmune diseases, fibromyalgia or myalgic encephalomyelitis. Inclusion commenced in 2006 and the study was closed after a minimum follow up of 5 years for all patients, with a maximum follow-up period of 10 years.

The study of Cohen Tervaert reported on symptoms suggestive of a (systemic autoimmune disease in the presence of a PP mesh [9]. Autoimmune disease in the presence of a PP implant in this study was defined as fulfillment of the criteria for the diagnosis of autoimmune/inflammatory syndrome induced by adjuvants (ASIA); Shoenfeld's criteria.[18] (Appendix B). Data were collected at presentation to an autoimmune clinic, no further follow-up was described.

Table 2. Summary of included studies

Authors	No. of patients	Inclusion Criteria	Age (years)	FU time	Results
Chugtai et al., 2017	N=12 716 mesh hernia N= 25 432 Colonoscopy	Inclusion: Patients undergoing PP mesh inguinal hernia repair. For control: patients undergoing colonoscopy.	Cohort: 57.8 (12.8)* Control: 57.8 (12.8)*	At 6 months, 1 year, 2 years and during the entire FU period (average was 6 years)	**Cohort:** 188 patients (1.5%) had developed SAID at the end of follow-up. **Control:** 413 patients (1.6%) had developed autoimmune disease at the end of follow-up. **Result:** Adjusted OR 0.91; 95%CI (0.76-1.09) No association was found between hernia mesh repair and the development of SAID at 6 months, 1 year and 2 year FU.
Chugtai et al., 2017	N= 1507 mesh N= 3014 Colonoscopy N=1375 Hysterectomy	Inclusion: Women undergoing mesh POP-repair. For control: Women undergoing screening colonoscopy (non-surgical cohort) or hysterectomy for benign gynecologic or Urogynaecologie indications.	Cohort: 60.4 (11.5)* Control: 60.4 (11.6)*	At 6 months, 1 year, 2 years and during the entire FU period (average was 6 years)	**Mesh vs. Colonoscopy**: Mesh cohort: 2.8% of patients developed SAID. Control: 2.8% of patients developed SAID. Adjusted OR 0.91; 95%CI (0.62 - 1.34). **Mesh vs. vaginal hysterectomy:** Mesh cohort: 2.8% of patients developed autoimmune disease. Control: 3.2% of patients developed SAID. Adjusted OR 0.78; 95% CI (0.48 - 1.26)
Cohen Tervaert, 2018	N=40 (18 hernia, 4 TVT and 18 TVM)	Inclusion: Patients presenting to several autoimmune clinics, who had previously implanted polypropylene mesh.	49.5 (range 28-75)	Not explicitly described, symptoms of auto-immune disease were recorded at presentation at the clinic, including whether a patient had a PP implant	18 (45%) of patients were diagnosed with autoimmune disease.

Table 2. Summary of included studies *(continued)*

Authors	No. of patients	Inclusion Criteria	Age (years)	FU time	Results
Muller et al., 2021	N= 88 947 mesh surgery N= 3389 non-mesh surgery	Inclusion: Women having first time urinary incontinence surgery with mesh For control: women having first urinary incontinence surgery without mesh.	Mesh: 53.1 ± 12* Control: 52.2 ± 12*	Mesh group: 8.7 (6.8-8.7)¥ years. Non-mesh group: 9.9 (7.4-9.9)¥ years.	Cumulative incidence of autoimmune disease, fibromyalgia or myalgic encephalomyelitis: Mesh group: 8.1% at 10 years Non-mesh group: 9% at 10 years

*Mean (SD)

¥ Median (IQR)

Outcomes

Chughtai et al. performed two retrospective cohort studies with matched controls.[15, 16] In one study subjects were males who had undergone an inguinal hernia repair with mesh, the other study included women with a POP repair with mesh. The source of patients was the New York State Department of Health Statewide Planning and Research Cooperative System (SPARCS).[19]

The male subjects who were included in the mesh for herniorrhaphy study were matched with a control cohort, consisting of patients undergoing colonoscopy. Controls were excluded if they had a history of mesh-related procedures, a diagnosis of colorectal carcinoma within one month of the colonoscopy or a previous diagnosis of SAID.

In total 12,716 men with a history of (mesh) herniorrhaphy were matched with 25,432 patients that had a colonoscopy. SAID was diagnosed in 188 (1.5%) in the mesh group. In the control group, 413 patients (1.6%) had developed SIAD at the end of follow-up. The adjusted OR was 0.91 (95% CI 0.76-1.09). After matching, the authors concluded that inguinal mesh hernia repair was not associated with the development of SAID.[16]

The women who have been enrolled in the POP with mesh repair study were matched with two cohorts of controls: a surgical and a non-surgical cohort. Controls were either women with a vaginal hysterectomy in their medical history for benign gynecological or urogynaecological conditions (surgical cohort) or women who had an indication for a screening colonoscopy (non-surgical cohort).

2102 women with a mesh-repair for POP were included. These were matched with 37298 women in the non-surgical control cohort and 7338 women in the surgical control cohort. This resulted in 1507 women with mesh-repair matched with 3014 colonoscopy patients and 1375 women with mesh-repair matched with 1375 women with vaginal hysterectomy.

Subjects with a (concurrent) history of autoimmune disease, malignancy, mesh-related procedures or prior pelvic floor surgery, were excluded. An additional exclusion criterion for the non-surgical cohort was inflammatory bowel disease. In the surgical control cohort women with endometrial hyperplasia with atypia, abnormal vaginal bleeding, or benign ovarian pathology were excluded.

In total SAID was diagnosed in 59 women (2.8%) after prolapse with mesh repair, in 1060 women (2.8%) after colonoscopy and in 235 women (3.2%) that had a history of vaginal hysterectomy.

After individual matching by demographics, date of the procedure and comorbidities, no increased risk of developing SAID after a mesh implantation for POP was found. The

adjusted OR was 0.91 (95% CI 0.62-1.34) when comparing to the colonoscopy group and 0.78 (95% CI 0.48-1.26) when comparing to the vaginal hysterectomy group.

Muller et al. [17] performed a national cohort study to compare the incidence of SAID in women having SUI surgery with and without mesh. Patients who had SUI surgery in the English NHS between 2006 and 2013 were included from an administrative database called the Hospital Episode Statistics.

Women were excluded if they had a record of SUI surgery in the previous 3 years or had a history of autoimmune disease, fibromyalgia or myalgic encephalomyelitis within this timeframe.

In total 88,947 women with mesh surgery and 3389 women without mesh surgery for SUI were included. The cumulative incidence of autoimmune disease, fibromyalgia or myalgic encephalomyelitis was 8.1% (95% CI 7.9-8.3%) in the mesh cohort and 9.0% (95% CI 8.0-10.1%) in the control group. The adjusted HR was 0.89 (95% CI 0.79-1.01; p=0.07).

This study did not demonstrate an increased risk of systemic disease after mesh implantation for SUI.

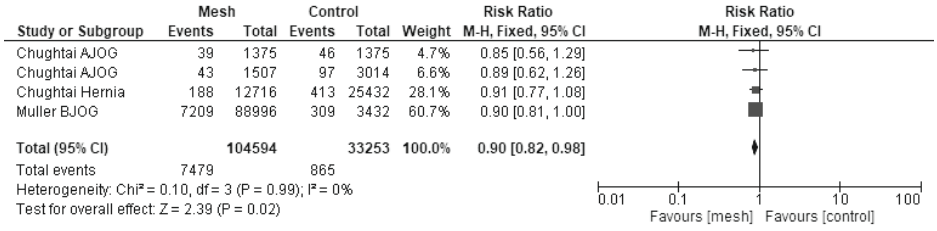
Finally, we included the study of Cohen Tervaert.[9] This study described 40 patients with systemic complaints in the presence of a PP mesh implant, that were selected out of a cohort of 714 patients that presented to the authors' autoimmune clinic. Patients were classified as suffering from autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome) when they fulfilled Shoenfeld's criteria.(Appendix B)[18]

The author described that in 24 out of 40 of the included patients their symptoms started within 1 year after mesh implantation. Ten out of 40 subjects developed ASIA between 1 and 3 years after the implantation of PP, and in 6 patients these symptoms developed later than 3 year after PP implantation. Eighteen out of 40 patients were diagnosed with an International Classification of Diseases (ICD) coded autoimmune disease.

Synthesis of results

A meta-analysis has been performed comparing the outcomes of appropriate studies. The meta-analysis shows no statistically significant association when comparing development of systemic disease after PP implantation and control groups. The Calculated risk ratio 0.9 (95% CI 0.82-0.98) concerning the mesh group; Fig. 2.

Figure 2. Forest plot of comparison: polylpropylene mesh versus no mesh, outcome: systemic auto-immune disorder(s)



Discussion

In current days, there is a growing concern about the use of PP mesh implants due to mesh-related complications. Some complications have a causal relation with the mesh implants, such as mesh exposure or erosion. In other complications attributed to mesh, such as systemic autoimmune syndromes, this causal relationship remains questionable. The present systematic review aimed at gathering the best scientific evidence currently available regarding the possible association between PP implants for inguinal hernia, ventral hernia or pelvic floor surgery and the development of systemic autoimmune syndromes. The available evidence is scant and should therefore be interpreted with caution. Nonetheless, there appears to be insufficient evidence to conclude an association between PP implants and development of systemic autoimmune syndromes.

The pooled data of Chughtai and Muller et al. showed a RR of systemic autoimmune disorders of 0.9 (95% CI 0.82-0.98) in the PP group. The incidence of systemic autoimmune disorders was 1.5% in the herniorrhaphy mesh group, 2.8% in the POP mesh group and 8.1% in the SUI mesh group. This is comparable with the overall prevalence of autoimmune diseases in the general population, which is estimated to be 3.2-9.4%.[15, 16, 20-22] This is in line with a recent review of Clancy et al. on assessing evidence regarding systemic and autoimmune effects of PP mesh in inguinal hernia repair. The authors found no evidence to link PP with systemic autoimmune syndromes.[10]

Thomas et al. performed a review examining the inflammatory response of PP implantation on its host. They found that the inflammatory response persists long after implantation, but no reports were found demonstrating systemic changes due to the implantation of a mesh.[23]

Since the available evidence does not show an association between PP mesh implants and the development of systemic autoimmune syndromes, one might wonder why this association has been suggested. This speculation has arisen on consumer websites and

discussion platforms, where a multitude of systemic complaints are considered to be related to mesh implants.[24, 25]

Mesh implantation triggers a cascade of reactions. The injury at implantation induces a blood-material interaction resulting in provisional matrix formation surrounding the biomaterial.[10, 26] Following this provisional matrix formation, an acute inflammatory response develops. In this phase neutrophil activity is enhanced and histamine and interleukin release from mast cells play an important role.[27] Subsequently, during the chronic inflammatory response, monocytes and lymphocytes can be found surrounding the mesh implant. Finally, there is a foreign body giant cell formation through fusion of these cells, as they fail to degrade the foreign body.[27]

The post-implantation inflammatory responses can elicit an upregulation of systemic inflammatory markers. Systemic levels of CRP and interleukin (IL)-6 are increased in the presence of a mesh.[10, 28] A persistent increased systemic response can theoretically account for the development of autoimmune symptoms.[29] The fact that studies on CRP and IL levels after mesh implantation show that these levels return to normal values within seven days after mesh implantation, however, opposes this theory.[10, 28, 30]

Another hypothesis why mesh implants theoretically might be able to cause autoimmune syndromes, is that the PP is degraded and absorbed into the systemic circulation.[10] Evidence regarding this possibility is conflicting. Some studies suggest (partial) degradation [31-33], whereas other studies showed no degradation in explanted meshes, up to 14 years after implantation.[34, 35]

This review, of course, has its limitations. There are only a few clinical studies regarding this subject. The applied search strategy resulted in only four reports on this topic, even though a comprehensive systematic search has been carried out. It is possible that the small number of studies relevant for this review are attributed to publication bias.

The included studies also had their flaws. Both studies of Chughtai[15, 16] had a minimal risk of bias, but still could have been affected by selection bias. Both studies used the SPARC database for patient selection.[19] This was an administrative database. Clinical data is not available and there is a risk that procedures and diagnosis of autoimmune diseases have been miscoded or missed. Furthermore, all registered inguinal hernia repairs were assumed to have undergone a PP mesh-based repair. This implies that some cases might not have had a PP mesh implant.

The risk of bias of the study of Muller et al [17] was low, but since an administrative database was used to select patients this can have inflicted selection bias. Another limitation, as described by the authors is the fact that the data was restricted to hospital admission

records. Outpatient data or data of primary care were not included, although this was similar for both the mesh and non-mesh group.

The study of Cohen Tervaert [9] was limited by the fact that the outcome was present at start of the study. Cases were selected from a population with an alleged autoimmune syndrome (ASIA). The paper described a relatively small size of 40 patients (out of 714) that had PP mesh implanted. Control groups and follow-up were lacking. A diagnostic tool developed for the diagnosis of ASIA has been extrapolated to patients with PP mesh implants. When using a diagnostic test it should be validated. This diagnostic tool has neither been developed for patients with mesh implants, nor has it been validated for this category of patients.

At last, another limitation of the current systematic review involves the partial overlapping of patients in the meta-analysis. The paper of Chughtai involved two control groups and cases were matched with these controls.[15] It remains uncertain, if not likely, that some patients with PP implants were incorporated in both analyses and consequently, in the present meta-analysis.

Conclusion

There is insufficient evidence to conclude that a causal association between PP mesh implants and the development of autoimmune syndromes exists, but consumer websites keep speculating on this association resulting in a lot of patient distress.

We propose a cross-sectional or cohort study measuring the immune status of patients prior to PP mesh implantation. In patients developing systemic complaints, the immune status could be examined again and compared with baseline. This will also enable examination of the potential pathophysiology of systemic complaints. Until such a study has been carried out, physicians should not suggest that PP implants possibly cause autoimmune syndromes. Such suggestions can distress patients, making them ask for operative interventions without a proper indication that can possibly harm them. Instead, physicians should discuss with their patients that the available evidence does not demonstrate a causal association between PP implants and autoimmune syndromes.

Appendix A: Search strategy

Medline (ovid)

Database(s): Ovid MEDLINE(R) ALL 1946 to November 22, 2021	
#	Searches
1	exp Pelvic Organ Prolapse/
2	exp Uterine Prolapse/
3	exp Hernia, Ventral/
4	exp Hernia, Inguinal/
5	exp Urinary Incontinence, Stress/
6	exp Cystocele/
7	exp Hernia, Abdominal/
8	exp Rectocele/
9	exp Herniorrhaphy/
10	((pelvi* or uterin* or uterus or urogenital* or vagin* or inguinal* or groin* or ventral or apical or vagin* vault) adj3 (hernia or prolaps*)).ti,ab,kf.
11	(colpoplast* or colporrhaph* or hernioplast* or hernioerhaph* or hernia* repair* or prolaps* repair*).ti,ab,kf.
12	(groin hernia* or inguinal hernia* or hernia inguinal or pelvic prolaps* or pelvic organ prolaps* or urinary stress incontinenc* or ventral hernia* or vagin* hernia or vagin* prolaps* or cystocele or enterocele or rectocele or vaginal vault prolaps* or anterior wall prolaps* or posterior wall prolaps* or middle compartment prolaps*).ti,ab,kf.
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	exp Polypropylenes/
15	Surgical Mesh/
16	(propene polymer* or poly-propylen* or propylene polymer* or polypropylen* or hernia* mesh or prolaps* mesh or surgical mesh).ti,ab,kf.
17	((Gynemesh or Coloplast or Restorelle or apogee perigee or Elevate or avaulta or prolift, IVS or MiniArc or Altis or Ajust, RetroArc or Bard Align) adj5 (poly-propylene* or polypropylen* or POP or mesh or vagin* repair* or prolaps* repair* or vagin* surg* or pelvic* surg*)).ti,ab,kw.
18	14 or 15 or 16 or 17
19	exp Autoimmunity/
20	exp Autoimmune Diseases/
21	exp Systemic Inflammatory Response Syndrome/
22	Inflammation/
23	exp Foreign-Body Reaction/
24	((chronic* or systemic or persist*) adj3 (inflammat* or immun*)).ti,ab,kf.
25	((immun* or inflammat* or autoimmun* or auto-immun*) adj3 (respons* or activat* or syndrome)).ti,ab,kf.
26	(autoimmun* or auto-immun* or autoinflam* or auto-inflam* or systemic inflam* or foreign body reaction or chronic* inflamm* or ASIA syndrome).ti,ab,kf.
27	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28	13 and 18 and 27

Embase (ovid)

Database(s): Ovid MEDLINE(R) ALL 1946 to November 22, 2021	
#	Searches
1	exp Pelvic Organ Prolapse/
2	exp Uterine Prolapse/
3	exp Hernia, Ventral/
4	exp Hernia, Inguinal/
5	exp Urinary Incontinence, Stress/
6	exp Cystocele/
7	exp Hernia, Abdominal/
8	exp Rectocele/
9	exp Herniorrhaphy/
10	((pelvi* or uterin* or uterus or urogenital* or vagin* or inguinal* or groin* or ventral or apical or vagin* vault) adj3 (hernia or prolaps*)).ti,ab,kf.
11	(colpoplast* or colporrhaph* or hernioplast* or hernioerhaph* or hernia* repair* or prolaps* repair*).ti,ab,kf.
12	(groin hernia* or inguinal hernia* or hernia inguinal or pelvic prolaps* or pelvic organ prolaps* or urinary stress incontinenc* or ventral hernia* or vagin* hernia or vagin* prolaps* or cystocele or enterocele or rectocele or vaginal vault prolaps* or anterior wall prolaps* or posterior wall prolaps* or middle compartment prolaps*).ti,ab,kf.
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	exp Polypropylenes/
15	Surgical Mesh/
16	(propene polymer* or poly-propylen* or propylene polymer* or polypropylen* or hernia* mesh or prolaps* mesh or surgical mesh).ti,ab,kf.
17	((Gynemesh or Coolest or Restorable or apogee perigee or Elevate or vault or prolife, IVS or Maniac or Altos or Adjust, Retro Arc or Bard Align) adj5 (poly-propylene* or polypropylene* or POP or mesh or vain* repair* or prolapse* repair* or vain* surge* or pelvic* surge*)).ti,ab,kw.
18	14 or 15 or 16 or 17
19	exp Autoimmunity/
20	exp Autoimmune Diseases/
21	exp Systemic Inflammatory Response Syndrome/
22	Inflammation/
23	exp Foreign-Body Reaction/
24	((chronic* or systemic or persist*) adj3 (inflammat* or immun*)).ti,ab,kf.
25	((immun* or inflammat* or autoimmun* or auto-immun*) adj3 (respons* or activat* or syndrome)).ti,ab,kf.
26	(autoimmun* or auto-immun* or autoinflam* or auto-inflam* or systemic inflam* or foreign body reaction or chronic* inflamm* or ASIA syndrome).ti,ab,kf.
27	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28	13 and 18 and 27

Scopus

TITLE-ABS-KEY (“pelvic organ Prolaps*” OR “uterine Prolaps*” OR “ventral hernia*” OR “inguinal hernia*” OR “urinary stress incontinenc*” OR cystocele OR rectocele OR enterocele OR “vaginal vault prolaps*” OR “apical prolaps*” OR “anterior wall prolapse*” OR “posterior wall prolaps*” OR “middle compartment prolaps*” OR herniorrhaphy OR colporrhaphy) OR (TITLE-ABS-KEY (pelvi* OR uterin* OR uterus OR urogenital* OR vagin* OR inguinal* OR groin* OR ventral OR apical OR “vagin* vault”) W/3 (hernia OR prolaps*)) AND TITLE-ABS-KEY (“propene polymer*” OR “poly-propylen*” OR “propylene polymer*” OR polypropylen* OR “hernia* mesh” OR “prolaps* mesh” OR “surgical mesh”) OR TITLE-ABS-KEY (gynemesh OR coloplast OR restorelle OR “apogee perigee” OR elevate OR avaulta OR prolift OR ivs OR miniarc OR altis OR ajust OR retroarc OR “Bard Align”) W/3 (“poly-propylene*” OR polypropylen* OR pop OR mesh OR “vagin* repair*” OR “prolaps* repair*” OR “vagin* surg*” OR “pelvic* surg*”) AND TITLE-ABS-KEY(Autoimmunity or “autoimmune Diseas*” or “Systemic Inflammatory Response Syndrome” or “inflammation” or “Foreign-Body Reaction” or “Foreign Body Reaction” or “chronic* inflamm*” or “ASIA syndrome”) OR TITLE-ABS-KEY((chronic* or systemic or persist*) W/3 (inflammat* or immun*))

Web of science	
#1	TS=(“pelvic organ Prolaps*” or “uterine Prolaps*” or “ventral hernia*” or “inguinal hernia*” or “urinary stress incontinenc*” or cystocele or rectocele or enterocele or “vaginal vault prolaps*” or “apical prolaps*” or “anterior wall prolapse*” or “posterior wall prolaps*” or “middle compartment prolaps*” or herniorrhaphy or colporrhaphy)
#2	TI=(“pelvic organ Prolaps*” or “uterine Prolaps*” or “ventral hernia*” or “inguinal hernia*” or “urinary stress incontinenc*” or cystocele or rectocele or enterocele or “vaginal vault prolaps*” or “apical prolaps*” or “anterior wall prolapse*” or “posterior wall prolaps*” or “middle compartment prolaps*” or herniorrhaphy or colporrhaphy) or AB=(“pelvic organ Prolaps*” or “uterine Prolaps*” or “ventral hernia*” or “inguinal hernia*” or “urinary stress incontinenc*” or cystocele or rectocele or enterocele or “vaginal vault prolaps*” or “apical prolaps*” or “anterior wall prolapse*” or “posterior wall prolaps*” or “middle compartment prolaps*” or herniorrhaphy or colporrhaphy)
#3	AB=((pelvi* or uterin* or uterus or urogenital* or vagin* or inguinal* or groin* or ventral or apical or “vagin* vault”) near/3 (hernia or prolaps*))
#4	((#3) OR #2) OR #1
#5	TS=(Polypropylenes or “Surgical Mesh”)
#6	TI=(“propene polymer*” or “poly-propylen*” or “propylene polymer*” or polypropylen* or “hernia* mesh” or “prolaps* mesh” or “surgical mesh”) or AB=(“p-ropene polymer*” or “poly-propylen*” or “propylene polymer*” or polypropylen* or “hernia* mesh” or “prolaps* mesh” or “surgical mesh”)
#7	AB=((Gynemesh or Coloplast or Restorelle or “apogee perigee” or Elevate or avaulta or prolift or IVS or MiniArc or Altis or Ajust or RetroArc or “Bard Align”) near/3 (“poly-propylene*” or polypropylen* or POP or mesh or “vagin* repair*” or “prolaps* repair*” or “vagin* surg*” or “pelvic* surg*”))
#8	((#5) OR #6) OR #7
#9	TS=(Autoimmunity or “autoimmune Diseas*” or “Systemic Inflammatory Response Syndrome” or “inflammation” or “Foreign-Body Reaction” or “Foreign Body Reaction” or “chronic* inflamm*” or “ASIA syndrome”)
#10	TI=((immun* or inflammat*) near/3 (respons* or activat* or syndrome*)) or AB=((immun* or inflammat*) near/3 (respons* or activat* or syndrome*))
#11	TI=(Autoimmunity or “autoimmune Diseas*” or “Systemic Inflammatory Response Syndrome” or “inflammation” or “Foreign-Body Reaction” or “Foreign Body Reaction” or “chronic* inflamm*” or “ASIA syndrome”) or AB=(Autoimmunity or “autoimmune Diseas*” or “Systemic Inflammatory Response Syndrome” or “inflammation” or “Foreign-Body Reaction” or “Foreign Body Reaction” or “chronic* inflamm*” or “ASIA syndrome”)
#12	((#9) OR #10) OR #11
#13	((#4) AND #8) AND #12

Appendix B:

Suggested Criteria for the diagnosis of autoimmune/inflammatory syndrome induced by adjuvants (ASIA).
Major Criteria:
• Exposure to an external stimuli (infection, vaccine, silicone, adjuvant) prior to clinical manifestations. • The appearance of 'typical' clinical manifestations: – Myalgia, Myositis or muscle weakness – Arthralgia and/or arthritis – Chronic fatigue, un-refreshing sleep or sleep disturbances – Neurological manifestations (especially associated with demyelination) – Cognitive impairment, memory loss – Pyrexia, dry mouth • Removal of inciting agent induces improvement • Typical biopsy of involved organs
Minor Criteria:
• The appearance of autoantibodies or antibodies directed at the suspected adjuvant • Other clinical manifestations (i.e. irritable bowel syn.) • Specific HLA (i.e. HLA DRB1, HLA DQB1) • Evolvement of an autoimmune disease

Shoenfeld Y, Agmon-Levin N. 'ASIA' - autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmun* 2011;**36**(1): 4-8

References:

1 D. Altman, T. Vayrynen, M. E. Engh, S. Axelsen, C. Falconer, et al. *Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse*. N Engl J Med 2011;364(19):1826-36.

2 I. L. Lichtenstein, A. G. Shulman & P. K. Amid. *Use of mesh to prevent recurrence of hernias*. Postgraduate Medicine 1990;87(1):155-60.

3 I. L. Lichtenstein. *Herniorrhaphy. A personal experience with 6,321 cases*. Am J Surg 1987;153(6):553-9.

4 J. M. Faylona. *Evolution of ventral hernia repair.* Asian J Endosc Surg 2017;10(3):252-58.

5 U. Ulmsten. *An introduction to tension-free vaginal tape (TVT) - A new surgical procedure for treatment of female urinary incontinence*. International Urogynecology Journal 2001;12(SUPPL. 2):S3-S4.

6 C. B. Iglesia, D. E. Fenner & L. Brubaker. *The use of mesh in gynecologic surgery.* International Urogynecology Journal 1997;8(2):105-15.

7 W. A. Zwaans, C. W. Perquin, M. J. Loos, R. M. Roumen & M. R. Scheltinga. *Mesh Removal and Selective Neurectomy for Persistent Groin Pain Following Lichtenstein Repair.* World J Surg 2017;41(3):701-12.

8 C. R. Kowalik, M. M. Lakeman, J. E. Oryszczyn & J. P. Roovers. *Reviewing Patients Following Mesh Repair; The Benefits*. Gynecol Obstet Invest 2016

9 J. W. Cohen Tervaert. *Autoinflammatory/autoimmunity syndrome induced by adjuvants (Shoenfeld's syndrome) in patients after a polypropylene mesh implantation*. Best Pract Res Clin Rheumatol 2018;32(4):511-20.

10 C. Clancy, P. Jordan & P. F. Ridgway. *Polypropylene mesh and systemic side effects in inguinal hernia repair: current evidence*. Ir J Med Sci 2019;188(4):1349-56.

11 D. Moher, A. Liberati, J. Tetzlaff, D. G. Altman & P. Group. *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement*. PLoS Med 2009;6(7):e1000097.

12 C. R. Kowalik, S. E. Zwolsman, M. P. Jonker & J. P. W. R. Roovers. *Is er verband tussen polypropyleenimplantaten en het ontstaan van auto-immuunziekten?* Nederlands Tijdschrift voor Obstetrie en Gynaecologie (NTOG) 2020;20(2):70-73.

13 M. Ouzzani, H. Hammady, Z. Fedorowicz & A. Elmagarmid. *Rayyan-a web and mobile app for systematic reviews*. Syst Rev 2016;5(1):210.

14 S. B. Wells GA, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp2021.

15 B. Chughtai, A. Sedrakyan, J. Mao, K. S. Eilber, J. T. Anger, et al. *Is vaginal mesh a stimulus of autoimmune disease?* Am J Obstet Gynecol 2017;216(5):495 e1-95 e7.

16 B. Chughtai, D. Thomas, J. Mao, K. Eilber, J. Anger, et al. *Hernia repair with polypropylene mesh is not associated with an increased risk of autoimmune disease in adult men*. Hernia 2017;21(4):637-42.

17 P. Muller, I. Gurol-Urganci, R. Thakar, M. R. Ehrenstein, J. Van Der Meulen, et al. *Impact of a mid-urethral synthetic mesh sling on long-term risk of systemic conditions in women with stress urinary incontinence: a national cohort study.* BJOG 2021

18 Y. Shoenfeld & N. Agmon-Levin. *'ASIA' - autoimmune/inflammatory syndrome induced by adjuvants*. J Autoimmun 2011;36(1):4-8.

19 New York State Department of Health. Statewide Planning adn Research Cooperative System (SPARCS). 2014 [Available from: www.health.ny.gov/statistics/sparcs/.

20 G. S. Cooper & B. C. Stroehla. *The epidemiology of autoimmune diseases*. Autoimmun Rev 2003;2(3):119-25.

21 G. S. Cooper, M. L. Bynum & E. C. Somers. *Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases*. J Autoimmun 2009;33(3-4):197-207.

22 W. W. Eaton, N. R. Rose, A. Kalaydjian, M. G. Pedersen & P. B. Mortensen. *Epidemiology of autoimmune diseases in Denmark*. J Autoimmun 2007;29(1):1-9.

23 D. Thomas, M. Demetres, J. T. Anger & B. Chughtai. *Histologic Inflammatory Response to Transvaginal Polypropylene Mesh: A Systematic Review*. Urology 2018;111:11-22.

24 S. K. ASIA Syndroom 2018 [Available from: https://www.meshedup.eu/asia-syndroom/ accessed 30-03-21 2021.

25 W. N. The Links Between Surgical Mesh Complications and the Development of Autoimmune Diseases 2013 [Available from: https://www.meshmedicaldevicenewsdesk.com/articles/the-links-between-surgical-mesh-complications-and-the-development-of-autoimmune-diseases accessed 30-03-2021 2021.

26 J. M. Anderson, A. Rodriguez & D. T. Chang. *Foreign body reaction to biomaterials*. Semin Immunol 2008;20(2):86-100.

27 H. Patel, D. R. Ostergard & G. Sternschuss. *Polypropylene mesh and the host response*. Int Urogynecol J 2012;23(6):669-79.

28 D. Kokotovic, J. Burcharth, F. Helgstrand & I. Gogenur. *Systemic inflammatory response after hernia repair: a systematic review*. Langenbecks Archives of Surgery 2017;402(7):1023-37.

29 K. Ishihara & T. Hirano. *IL-6 in autoimmune disease and chronic inflammatory proliferative disease*. Cytokine Growth Factor Rev 2002;13(4-5):357-68.

30 G. Di Vita, S. Milano, M. Frazzetta, R. Patti, V. Palazzolo, et al. *Tension-free hernia repair is associated with an increase in inflammatory response markers against the mesh*. American Journal of Surgery 2000;180(3):203-07.

31 D. R. Ostergard. *Polypropylene vaginal mesh grafts in gynecology*. Obstetrics and Gynecology 2010;116(4):962-66.

32 A. Imel, T. Malmgren, M. Dadmun, S. Gido & J. Mays. *In vivo oxidative degradation of polypropylene pelvic mesh*. Biomaterials 2015;73:131-41.

33 C. R. Costello, S. L. Bachman, B. J. Ramshaw & S. A. Grant. *Materials characterization of explanted polypropylene hernia meshes*. Journal of Biomedical Materials Research - Part B Applied Biomaterials 2007;83(1):44-49.

34 S. F. Thames, M. D. Blanton, E. B. Williams, J. B. White, K. E. Stoner, et al. *Implantation Time Has No Effect on the Morphology and Extent of Previously Reported "Degradation" of Prolene Pelvic Mesh*. Female Pelvic Med Reconstr Surg 2020;26(2):128-36.

35 S. F. Thames, J. B. White & K. L. Ong. *The myth: in vivo degradation of polypropylene-based meshes*. Int Urogynecol J 2017;28(2):285-97.

Chapter 6

Results of an innovative bulking agent in patients with stress urinary incontinence who are not optimal candidates for mid-urethral sling surgery

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Abstract

Background/ aims
To assess the efficacy and safety of peri-urethral bulking injections (PBI) with an innovative bulking material (PDMS-U) in women with stress-urinary incontinence (SUI) who are not optimal candidates for mid-urethral sling surgery.

Methods
A prospective study was performed in women with SUI who, for several reasons, have a relative contraindication for a mid-urethral sling procedure.

These reasons include: (I) recurrent SUI after a prior SUI surgical procedure; (II) a history of oncologic gynaecological surgery; (III) a history of neurologic disease resulting in voiding problems; (IV) a maximal flow rate of less than 15 mL per second or; (V) women with a contraindication for surgery with general or regional anaesthesia. All women were treated with PBI consisting of PDMS-U, a bulking agent that polymerizes in situ. The primary outcome was subjective improvement, defined as “a little better” to “very much better” on the PGI-I. Secondary outcomes included objective cure, disease specific quality of life and adverse events.

Results
Subjective improvement was reported by 18 (90%) of the 20 included patients. The subjective cure rate was 56% and the objective cure rate was 65%. There was a statistically significant improvement of all domain scores of the UDI-6, IIQ-7 and PISQ-12 at 6 months follow up. Abnormal post voiding residual volume (>150mL) was the most common adverse event (40%), but persisted in only one patient, based on the patient’s preference for a catheter.

Conclusion
PBI with PDMS-U is a viable treatment option in women with a relative contra-indication for mid-urethral sling surgery.

Introduction

Stress urinary incontinence (SUI) is a significant clinical problem affecting approximately 20% of the female population.[1]

The gold standard for the surgical treatment of SUI, is the placement of a mid-urethral sling (MUS). Despite the high cure rates of MUS surgery, the search for less invasive, safe and still effective treatment modalities for SUI is ongoing.

Peri-urethral bulking injections (PBI) are a treatment modality with the benefit of occurring in an ambulatory setting, having a low complication rate and a fast recovery to normal daily activities. Up till now significant lower cure rates are seen in PBI when compared to MUS surgery. The hypothetical mechanism of action of PBI is that by the injection of bulking agents into the urethral submucosa, artificial urethral cushions are created that improve urethral coaptation and hence restore continence.[2] The ideal material for PBI should be non-immunogenic and biocompatible, causing a minimal inflammatory and fibrotic response, and the bulking material should be made of particles large enough to stay in situ, theoretically increasing the chance of a durable effect.[2]

An innovative bulking agent that recently has been introduced to the market is a biomaterial that is made of a vinyl dimethyl terminated polydimethylsiloxane (PDMS) polymer, tetrapropoxysilane cross-linking agent, platinum divinyltetramethyl siloxane complex catalyst, titanium dioxide radio-pacifying agent (Urolastic®, Urogyn BV, Nijmegen, the Netherlands), (PDMS-U). The unique feature of this bulking agent is that this material polymerises in situ forming a uniform elastomer that adapts itself to the environment during injection. This results in a large, non-biodegradable homogeneous mass that becomes encapsulated by the body as a whole and as a result the risk of migration decreases and the chance that the product is durable increases.

A few observational studies have been performed with PDMS-U. Two studies in women with predominantly primary SUI showed an overall success (defined as a decrease in the Stamey Score by 1 grade compared to the baseline continence status) of 89% after 12 months follow up and 66% after 24 months follow up, whereas respectively 68% and 45% of patients were dry after 12 and 24 months.[3, 4] Two reports on women with mostly recurrent SUI reported that 59% and 22% of patients were completely dry after 12 and 24 months of follow up respectively. [5, 6]

Product to product comparative studies with PDMS-U are not available. The results at 12 month follow up appear to be slightly better as compared to bulking agents made of polymers that are dispensed in a carrier gel, like Polyacrylamide hydrogel (PAHG) (Bulkamid®, Contura International A/S, Soeborg Denmark) and PDMS suspended in a carrier hydrogel (Macroplastique®, Cogentix Medical, Minnetonka, USA). Cure (dry) rates

with these longer used biomaterials have been reported to range between 24 to 47% at 12 months for Polyacrylamide hydrogel (PAHG) and 36% for PDMS after more than 18 months of follow up.[7 8, 9]

The exact indication for PBI has not been well established. Whereas some institutes offer this treatment to patients with mild symptoms who are not motivated for pelvic floor muscle therapy (PFMT) or had no benefit of PFMT, other centers -like ours- preserve PBI for the most severe cases.

In recent history new treatment modalities have been introduced and also implemented within urogynecology without thorough evaluation of safety and efficacy. We felt the need to properly evaluate this in situ polymerising bulking injection prior to implementing this treatment into routine clinical practice. For this reason we initiated a pilot study in women with a poor prognostic profile to be cured with a mid-urethral sling, aiming to evaluate safety and efficacy of this new bulking material.

Materials and Methods

We performed a prospective observational study in two Dutch teaching hospitals with a special interest in urogynecology. The medical ethics review committee of the Academic Medical Center in Amsterdam judged that the Medical Research Involving Human Subjects Act does not apply to this study.

Study population
We intended to select patients for whom MUS surgery would not be the optimal treatment. Indications for intervention included: (I) recurrent SUI after a prior SUI surgical procedure; (II) a history of oncologic gynaecological surgery; (III) a history of neurologic disease resulting in voiding problems; (IV) a maximal flow rate of less than 15 mL per second or; (V) women with a contraindication for surgery with general or regional anaesthesia.

Participants were women aged 18 years or older, with symptoms of SUI or stress-predominant mixed urinary incontinence (MUI). Exclusion criteria included pelvic organ prolapse (POP) beyond the hymen, indication for a concomitant surgical procedure, presence of a urinary tract infection (UTI), or a post voiding residual volume (PVR) of more than 150 mL.

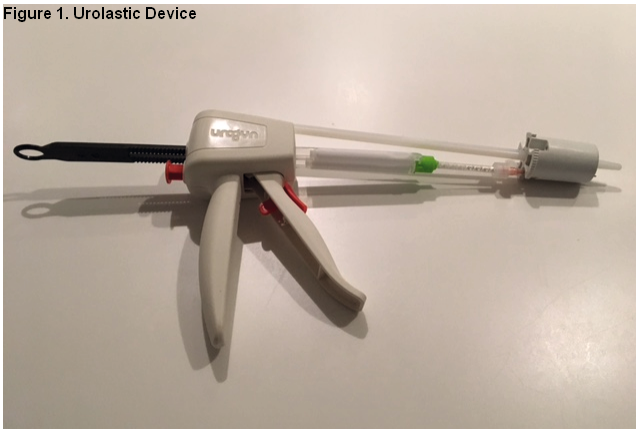
Women were screened for eligibility after finalizing the standardized diagnostic work-up. In both participating hospitals the protocol involves keeping a 48-hour diary to record drinking and micturition habits, a urinary dipstick test to screen for UTI, uroflowmetry, PVR measurement and pelvic examination to score genital prolapse according to the

POP- Quantification.[10] Prior to enrolment into the study, written informed consent was obtained from all patients.

Procedure

All women were treated with PDMS-U. The procedures were performed by two gynaecologists who have been trained to perform the PBI. Prior to the intervention the urine was checked for a UTI. When a UTI was suspected (a positive urinary stick for leucocytes and/or nitrate and symptoms of cystitis), the intervention was postponed until the infection had been treated. In one center women were given Ciprofloxacin 500mg orally as antibiotic prophylaxis one hour before the procedure, the other center performed the PBI without antibiotic prophylaxis.

Figure 1. Urolastic Device



Local analgesia was assured by application of peri–urethral injections with Lidocaine 1% at the intended injection sites. The compound was applied at 4 defined sites (10, 2, 5 and 7 o'clock) of the mid-urethra by use of a special device (Fig. 1). After positioning the device in the urethra, the injections were administered through the device. The amount of injected compound was set at 1.0 mL of compound at the 5 and 7 o' clock position and 0.8 mL of compound at the 2 and 10 o' clock position. After 6 weeks to several months, a repeat procedure could be performed in case the effect was suboptimal by injecting additional compound at the 3 and /or 9 o'clock position. Before discharge, PVR was measured after spontaneous voiding with a bladder scan. In case of incomplete voiding defined as a PVR of more than 150 mL, a 12 French Foley indwelling catheter was used to drain the bladder and if PVR of 150 mL persisted after 24-48 hours women commenced with clean intermittent catheterisation (CIC) until a PVR of less than 150 mL was obtained.

Measurements

Women were evaluated at baseline, 6 weeks, and 6 months follow up. The primary outcome was subjective improvement defined as responding in the range of "a little better" to "very much better" on the "Patient Global Impression of Improvement

Questionnaire" (PGI-I) at 6 months after surgery. The PGI-I is a global assessment question that has been validated to assess treatment response in women with SUI.[11]

Secondary outcomes included subjective cure, defined as "much better" and "very much better" on a 7 point Likert scale, objective cure assessed by a negative cough stress test (CST) with a comfortably filled bladder in the lithotomy position at 6 months follow up, disease specific quality of life related to micturition and sexual function, adverse events and re-interventions.

Health-related quality of life was assessed by asking all patients to complete three Dutch validated disease specific quality of life questionnaires at baseline, 6 weeks and 6 months of follow up. The short form Urogenital Distress Inventory (UDI-6), the short form Incontinence Impact Questionnaire (IIQ-7) and the short form Pelvic Organ Prolapse/ Urinary Incontinence Sexual Function Questionnaire (PISQ-12).

The UDI-6 and the IIQ-7 measure the impact of symptoms associated with lower urinary tract dysfunction on quality of life. The UDI-6 is divided into three domains: irritative, stress and obstructive/discomfort symptoms. The IIQ-7 measures the impact of micturition symptoms on different aspects of quality of life. The questions are divided into four domains: mobility, physical activity, social functioning and emotional health. Both UDI-6 and IIQ-7 scores range from 0-100, 0 identifying patients with no bother of micturition symptoms and 100 identifying patients who experience symptom distress. [12, 13]

The PISQ-12 is a validated and reliable short form that evaluates sexual functioning in women with POP and/ or urinary incontinence. It contains questions regarding physical, behavioral–emotive and partner-related aspects of sexual functioning. The sum score ranges from 0–48, with a higher score indicating better sexual functioning.[14]

Statistical analysis

Baseline and demographic data were reported using standard descriptive methods; Nominal data were described with frequencies and percentages, not normally distributed continuous data with median and interquartile range, and normally distributed continuous data with mean and standard deviation. The UDI-6, IIQ-7 and PISQ-12 scores were calculated as proposed by composers of the questionnaires.[13, 14] Comparisons of the CST, UDI-6, IIQ-7 and PISQ-12 before and after treatment were done using a non-parametric Wilcoxon signed rank tests for determining statistical significant differences in paired not normally distributed data. Statistical analysis has been performed using IBM SPSS Statistics 22.

Results

Study population

Twenty women were enrolled in the study between 2014 and 2015. Demographic data are depicted in Table 1. Of the women participating in the study sixteen women (80%) completed follow up of six months (study visit and questionnaires).

Procedure

The PBI was performed in an outpatient setting in 20 patients. Five women (25%) required a second procedure due to suboptimal outcome. In three of these women, bulking material had to be removed directly after the first procedure because of too superficial location (sub-epithelial) of the bulking material. The volume of injected PDMS ranged from 3.2 to 4.8 mL divided over all locations for the first procedure and from 0.8 to 1.6 mL for the second procedure. The median time between the first and subsequent procedure was 15 weeks (range 11-21 weeks).

TABLE 1. Baseline Characteristics and reasons for inclusion

Patient demographics	n = 20
Age (years) *mean (SD)**	61 (12)
Degree of SUI *n (%)*	
Drops	1 (6)
Shoots	8 (44)
More than shoots	9 (50)
Parity *median (IQR)***	2 (2-3)
Current smoker *n (%)*	4 (20)
Reason for inclusion *n (%)*	
Stress incontinence	12 (60)
Mixed incontinence	8 (40)
Recurrent SUI and surgical history *n (%)*	8 (40)
Burch colposuspension	1 (5)
Burch colposuspension + Mid-urethral sling	1 (5)
Mid-urethral sling	4 (20)
Repeat Mid-urethral sling	2 (10)
Bulking injections	1 (5)
Oncological history *n (%)*	6 (30)
Radical hysterectomy (cervical carcinoma)	5 (25)
Radical local excision (vulvar carcinoma)	1 (5)
Neurological history *n (%)*	2 (10)
Flow < 15 ml/sec *n (%)*	3 (15)
Contra-indication for total or regional anesthesia *n (%)*	1 (5)

*SD: standard deviation

**IQR: interquartile range

PGII

At 6 months follow up 18/20 (90%) of women reported subjective improvement. Two women who have not reported subjective improvement did not complete the PGI-I. One woman could not answer the PGI-I since she had a permanent indwelling catheter due to refractory mixed urinary incontinence. The other woman did not feel like filling out the questionnaires at her 6 months visit, since she had been diagnosed with ovarian carcinoma just prior to this appointment. She did consent to fill out the questionnaires one year after her PBI and reported "no change" on the PGI-I. Of the 18 women that reported subjective improvement, 10/18 (56%) were subjectively cured.

CST

At 6 months follow-up a negative CST was observed in 13/20 (65%) of patients (p<0.00), 4/20 (20%) had a positive CST, three women did not come for their 6 months appointment. Of these three non-responders, one woman had a permanent indwelling catheter, in one woman follow up was completed at 12 months post procedure. At that time her CST was positive. The third woman was contacted by phone and said to have been cured from her urinary incontinence.

Health-related quality of life

Health-related quality of life is depicted in Table 2. UDI-6 and IIQ-7 scores in all subscales improved significantly at 6 months of follow up as compared to scores at baseline (UDI-6 total p <0.00 and IIQ-7 p <0.00). Half of the included women were sexually active at baseline. PISQ-12 scores of these women improved significantly after 6 months follow up (p=0.04).

Adverse events

Adverse events related to the procedure are shown in Table 3. In three women, bulking agent was removed directly after the procedure because it was judged the material was positioned to superficial, just beneath the vaginal epithelium. Two of these women reported they had lost more material at home and one of them had an exposure at the first follow-up visit. The exposure could be managed in an outpatient setting by removing the exposed material.

Incomplete voiding immediately after the procedure was the most frequent adverse event 8/20 (40%) and was most common in 5/8 (63%) women with recurrent SUI after a prior SUI surgical procedure. Six women were treated with an indwelling catheter followed by CIC, after which bladder emptying normalized within a median of 12 days (range 2 to 17 days). One woman had to undergo partial removal of the bulking material to solve incomplete voiding and one woman preferred to continue CIC as she was very happy about being dry after the procedure.

TABLE 2. Secondary Outcomes

	Baseline	FU*6 weeks	FU 6 months	Treatment effect†
UDI-6 ˜ *mean (SD**)*	n =20	n =18	n =16	
Irritative subscale	61 ±32	38 ± 30	32 ± 32	0.01
Stress subscale	86 ± 15	48 ± 34	38 ± 29	<0.01
Obstructive subscale	31 ± 21	21 ± 24	13 ± 19	0.01
IIQ-7‡ *mean (SD)*	n =20	n =18	n =17	
Physical activity	68 ± 23	34 ± 27	24 ± 27	<0.01
Mobility	63 ± 31	33 ± 37	27 ± 30	<0.01
Social functioning	60 ± 32	30 ± 36	24 ± 31	<0.01
Emotional health	57 ± 35	27 ± 33	21 ± 33	<0.01
	n=8	n=5	n=6	
PISQ-12 ¥ summary score	30 ± 8	39 ± 3	35 ± 5	0.04

* FU: follow-up

** SD: standard deviation

˜ UDI-6: Urogenital Distress Inventory

‡ IIQ7-: Incontinence Impact Questionnaire

¥ PISQ12-: Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire

† Significance cut-off at p<0.05 after 6 months follow up

TABLE 3. Per- and post procedure complications

Complication	
Per-procedure complications	
Hematoma	1 (5)
PDMS[a] at epithelial surface (requiring direct excision)	3 (15)
Pain	2 (10)
Postoperative complications	
PVR (>150 ml)	8 (40)
CAD[b] 24 hours	5 (25)
CAD 48 hours	1 (5)
CIC[c] days (median)	12 (2-17)
Exposure	1 (5)
Spontaneous loss of bulking material	2 (10)

[a]PDMS: Polydimethylsiloxane

[b]CAD: Catheter à demeure

[c]CIC: clean intermittent catheterization

Discussion

This study evaluates the efficacy and safety of an innovative PBI in women with SUI and a poor prognostic profile to be cured with MUS surgery. Our study shows a substantial subjective improvement in 90% of this specific category of patients, a subjective cure rate of 56% and a statistically significant improvement of disease specific quality of life. The surgical re-intervention rate was 25% for suboptimal outcome and 5% for incomplete bladder emptying.

The efficacy of PDMS-U is difficult to compare to other bulking agents used for second line treatment, due to differences in definition of success, type of bulking material used, and time of follow up.

The few studies that evaluated efficacy of other bulking agents as salvage therapy after prior sling placement report success rates varying between 35-43%. [15] [16, 17]

The most common adverse event in our study was incomplete voiding which occurred in 40% of subjects. This is in contrast with other studies reporting incomplete voiding in 13 to 17% of patients.[15, 17] A possible explanation can be the fact that the average amount of the applied bulking material was less in these studies, therefore probably causing less urethral obstruction.[15, 17] The high risk of incomplete voiding can also be attributed to the fact that patients treated with PBI after a previous MUS or patients with a poor prognostic profile have a high a priori risk. However, the incomplete bladder emptying resolved spontaneously after a short period of CIC in most subjects, which confirms the observation done in other studies evaluating bulking agents.[15, 17]

Three patients had multiple complications related to the location of the implant after injection (hematoma, bulking material at epithelial surface requiring direct excision, spontaneous loss of bulking material and exposure). Two of these patients had had pelvic surgery and radiotherapy because of cervical and rectal cancer. A possible explanation for these two women to have this combination of complications could be the fact that they had undergone radiotherapy. Radiation can negatively affect the quality of the epithelial layer of the vagina, compromise the vascularization and cause atrophic changes of the mucosa.[18] These radiation effects can theoretically be of influence on the tissue reaction after PBI, possibly attributing to the occurrence of adverse events. However, the numbers are too small to draw strong conclusions.

Some may argue that the adverse event rate we observed is concerning, since 25% needed a re-intervention for it. However, most of these re-interventions (20%) could be performed in the outpatient clinic. The cure rates and satisfaction rates were high. We conclude that the success rate of this bulking needs to be traded against the risk on

serious adverse events. The patient should be the one to decide whether she accepts the risks of a re-intervention.

A few design related issues need to be discussed:

A strength of this pilot study is that the PBI procedure was standardized with respect to the locations of injection and the amount of compound used. In PBI the amount of compound and exact location of injection are to the discretion of the surgeon, making comparison of outcome in patients difficult. Standardization of the technique of PBI enables assessment of efficacy of the PBI as a procedure instead of PBI as an individualized treatment.

Another strength is the selection of subjects with a poor prognostic profile to be cured by mid urethral sling surgery. These are the patients that have an indication for PBI according to international guidelines and therefore will be offered this therapy. These patients should be informed about the efficacy and morbidity of PBI, based on studies in patients with a similar profile, like this study, instead of patients with better prognostic profile and therefore possibly better outcome.

This study also has some limitations. We considered that studying 20 patients meets the requirements of performing an adequate pilot study. That indicates however that the generalizability of our data is limited. The next step is to design a comparative study, which is powered on the observations of this pilot study.

Some might argue the choice of a subjective outcome measurement as primary outcome. The PGI-I response, our primary outcome, correlates significantly with objective outcome like pad test results and the frequency of incontinence episodes, warranting the decision not to do a pad test to minimize patient effort to assess efficacy. [11] Furthermore, women's goals of treatment are personal and highly subjective.[19] As a consequence the primary outcome during evaluation should be a subjective outcome.

We decided to focus on improvement as our primary outcome, since we felt that these difficult to cure women would benefit of any kind of improvement. This might have caused bias, since these women possibly reported improvement with the slightest change or a placebo effect could have been measured.

Conclusions

With this study, we have shown that PBI with PDMS-U is an effective treatment for SUI in a difficult to cure group of women with bothersome SUI. The high subjective improvement rate in such a difficult to treat group underlines the fact that PBI with PDMS-U should be offered as a treatment option to these women. If these results would be consistent in women with a normal profile, PBI could be offered as an alternative to MUS in women seeking treatment for SUI. Before PBI can be implemented in common practice and offered to all women presenting with bothersome SUI, efficacy and safety need to be studied more extensively.

References

1 B. K. Hunskar S. Epidemiology of urinary and faecal incontinence and pelvic organ prolapse. Incontinence volume 1, basic evaluation. 3rd International Consultation on Incontinence edition 2005. Health publication Ltd 2005,. Paris, 2013.

2 V. Kirchin, T. Page, P. E. Keegan, K. Atiemo, J. D. Cody, et al. *Urethral injection therapy for urinary incontinence in women*. Cochrane Database of Systematic Reviews 2012(2)

3 J. Zajda & F. Farag. *Urolastic-a new bulking agent for the treatment of women with stress urinary incontinence: outcome of 12 months follow up*. Adv Urol 2013;2013:724082.

4 J. Zajda & F. Farag. *Urolastic for the treatment of women with stress urinary incontinence: 24-month follow-up*. Cent European J Urol 2015;68(3):334-8.

5 K. Futyma, P. Miotla, K. Galczynski, W. Baranowski, J. Doniec, et al. *An Open Multicenter Study of Clinical Efficacy and Safety of Urolastic, an Injectable Implant for the Treatment of Stress Urinary Incontinence: One-Year Observation*. Biomed Res Int 2015;2015:851823.

6 K. Futyma, L. Nowakowski, K. Galczynski, P. Miotla & T. Rechberger. *Nonabsorbable urethral bulking agent - clinical effectiveness and late complications rates in the treatment of recurrent stress urinary incontinence after 2 years of follow-up*. Eur J Obstet Gynecol Reprod Biol 2016;207:68-72.

7 G. Lose, H. C. Sorensen, S. M. Axelsen, C. Falconer, K. Lobodasch, et al. *An open multicenter study of polyacrylamide hydrogel (Bulkamid(R)) for female stress and mixed urinary incontinence*. Int Urogynecol J 2010;21(12):1471-7.

8 E. R. Sokol, M. M. Karram & R. Dmochowski. *Efficacy and safety of polyacrylamide hydrogel for the treatment of female stress incontinence: a randomized, prospective, multicenter North American study*. J Urol 2014;192(3):843-9.

9 G. M. Ghoniem & C. J. Miller. *A systematic review and meta-analysis of Macroplastique for treating female stress urinary incontinence*. Int Urogynecol J 2013;24(1):27-36.

10 R. C. Bump, A. Mattiasson, K. Bo, L. P. Brubaker, J. O. DeLancey, et al. *The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction*. Am.J.Obstet. Gynecol. 1996;175(1):10-17.

11 I. Yalcin & R. C. Bump. *Validation of two global impression questionnaires for incontinence*. Am J Obstet Gynecol 2003;189(1):98-101.

12 E. Utomo, I. J. Korfage, M. F. Wildhagen, A. B. Steensma, C. H. Bangma, et al. *Validation of the Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) in a Dutch population*. Neurourol Urodyn 2015;34(1):24-31.

13 J. S. Uebersax, J. F. Wyman, S. A. Shumaker, D. K. McClish & J. A. Fantl. *Short forms to assess life quality and symptom distress for urinary incontinence in women: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program for Women Research Group*. Neurourol.Urodyn. 1995;14(2):131-39.

14 R. G. Rogers, K. W. Coates, D. Kammerer-Doak, S. Khalsa & C. Qualls. *A short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12)*. Int.Urogynecol.J.Pelvic. Floor.Dysfunct. 2003;14(3):164-68.

15 H. N. Lee, Y. S. Lee, J. Y. Han, J. Y. Jeong, M. S. Choo, et al. *Transurethral injection of bulking agent for treatment of failed mid-urethral sling procedures*. Int Urogynecol J 2010;21(12):1479-83.

16 L. W. Kim J, Lucioni A, Govier F, Kobashi K. *1360 Long-term efficacy and durability of durasphere urethral bulking after failed urethral sling for stress urinary incontinence*. The journal of Urology 2012;187(4):e522.

17 I. Zivanovic, O. Rautenberg, K. Lobodasch, G. von Bunau, C. Walser, et al. *Urethral bulking for recurrent stress urinary incontinence after midurethral sling failure*. Neurourol Urodyn 2016

18 K. Kirchheiner, R. A. Nout, J. C. Lindegaard, C. Haie-Meder, U. Mahantshetty, et al. *Dose-effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study.* Radiother Oncol 2016;118(1):160-6.

19 E. A. Elkadry, K. S. Kenton, M. P. FitzGerald, S. Shott & L. Brubaker. *Patient-selected goals: a new perspective on surgical outcome*. Am J Obstet Gynecol 2003;189(6):1551-7; discussion 57-8.

Chapter 7

Patients' satisfaction and safety of bulk injection therapy Urolastic® for treatment of stress urinary incontinence: a cross-sectional study

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Abstract

Background/ aims

Primary outcome was to evaluate patients' satisfaction after being treated with bulk injection therapy polydimethylsiloxane (PDMS) Urolastic® for stress urinary incontinence (SUI). Secondary outcomes were: subjective cure, objective cure, severity of SUI symptoms, complications and re-intervention rate and disease-specific quality of life. Furthermore, to determine if outcomes worsened during time-after-treatment (time-frames: 0-12, 13-24 and ≥25 months).

Methods

In a cross-sectional design, patients treated with Urolastic® were recruited for hospital revisit. The primary outcome, patients' satisfaction, was assessed by the surgical satisfaction questionnaire. Subjective cure, objective cure and severity of symptoms were assessed by the patients global impression of improvement, standardized cough stress test and Sandvik severity scale, respectively. Medical charts and face-to-face interviews were used to determine complications and re-interventions.

Results

110 patients participated, 87 revisited the hospital. Median follow-up was 25 months (IQR: 14;35 months). Patients' satisfaction rate was 51%. Subjective cure and objective cure were respectively 46% and 47%. Most prevalent complications were urinary retention (22%), pain (15%) and dyspareunia (15%). Exposure and erosion occurred in 7 and 5% respectively. Re-intervention rate of re-injection and excision of bulk material was 6% and 18% respectively. Objective cure significantly worsened during time-after-treatment (p=<0.05).

Conclusion

About half of the patients being treated with PDMS-U were satisfied and subjectively cured 2 years after treatment, although the majority still experienced symptoms of SUI. Most complications were mild and transient, however, in 18% excision of bulk material was indicated for severe or persistent complications such as pain, exposure or erosion.

Introduction

Symptoms of urinary incontinence (UI) are highly prevalent and can affect a patient's quality of life (QoI) severely. [1, 2] When involuntary urine leakage occurs during increased abdominal pressure such as coughing, sneezing or physical exertion, it is defined as stress UI (SUI) which comprises about half of UI cases.[3] Behavioral and pharmacological therapies, pelvic floor muscle exercises, vaginal devices (e.g. pessary) and surgical options such as synthetic slings, colposuspension, autologous sling surgery and bulking agents cover the treatment options for female SUI. Consensus statement of the European Urology Association and the European Urogynaecological Association conclude that synthetic slings have a good efficacy and acceptable morbidity, but alternative options must be considered.[4]

Urethral bulk injection therapy is an alternative non-invasive, ambulatory treatment that involves injecting a bulk material transurethral or peri-urethral, with or without urethroscopic view, in the mucosa of the urethra between the mid-urethra and bladder neck. The injected material gives resistance to the urine flow and thereby aims to prevent leakage of urine, although it is hypothesized that mid-urethral support is needed for the closure mechanism of the urethra as well.[5]

To date, randomized controlled trials comparing bulk injection therapy with other surgical options show significant lower objective cure rates regarding urethral bulk injection therapy.[6, 7]

Peri-urethral injection therapy polydimethylsiloxane Urolastic (PDMS-U) (Urogyn BV Nijmegen, The Netherlands) is one of the latest developed bulking agents and consists of a smooth, non-degradable biocompatible polymer texture. This unique character implies that the bulk material is not absorbed by the body and will stay positioned over time. Using a disposable injecting device, four depots of 0.8 to 1.0 cc are injected peri-urethral at 2, 5, 7, and 10 o'clock at the mid- urethral level, without cystoscopic control.

From 2011, multiple hospitals have included PDMS-U as standard treatment option for patients with SUI or mixed urinary incontinence (MUI). Objective and subjective success rates at 6 to 12 months follow-up varied from 59% to 89% and 35% to 90%, respectively.[8-10] At 2 years follow-up, objective cure rates of 33% to 66% were reported.[11, 12] Although the variety of used study outcomes, patient selection and the learning curve of the physician may have contributed to the wide range, the reported objective cure rate seemed to worsen with longer follow-up. Efficacy rates are in line with bulking agents "Macroplastique" and "Bulkamid" showing subjective success rates of 66% to 90% at 12 months follow-up and objective success rates of 25% to 73%.[13]

Safety studies show that patients treated with PDMS-U, compared with other bulking agents, were more likely to be indicated for excision of the bulk material due to complications like exposure or pain.[14] As there are no studies that investigated the patients' satisfaction or safety after 2 years follow-up, we have set up this cross-sectional study in a population of patients that have been treated with PDMS-U from 2014 up to 2018 through standard care. In this retrospective case series our primary aim was to determine patients' satisfaction. Other outcomes were: subjective cure, objective cure, severity of SUI symptoms, complications and re-interventions, and disease-specific QoL. Second, we aimed to determine if outcomes would worsen during time-after-treatment, following the time frames: 0 to 12 months, 13 to 24 months, and more than 25 months after treatment.

Materials and methods

A multi-centre, cross-sectional study was performed in four experienced centres. Site specific information is shown in Appendix 1. To evaluate the influence of a learning curve, only centres that had performed more than 20 PDMS-U procedures were considered to be eligible. The study was reviewed and approved by the ethical committee of all participating centres. The study population consisted of patients who had been treated with PDMS-U as part of standard care. Women more than or equal to 18 years who received PDMS-U as primary treatment for SUI, secondary for recurrent SUI, or MUI were found eligible. Patients were excluded if they had received PDMS-U for neurogenic bladder, participated in clinical studies or were incapable of giving informed consent.

Enrollment

Patients were informed about the study by a patient information leaflet. Patients who were willing to participate were asked to revisit the hospital. Written informed consent was obtained for subjects on the day of the revisit. Patients who declined participation could give consent to share information from their medical chart by means of an additional informed consent form.

Study procedure

All patients were asked to revisit the hospital where they had been treated. A paper questionnaire was used to obtain patients characteristics and determine the severity and impact of UI symptoms, complications, and re-interventions. In case patients were unable to revisit the hospital, a paper questionnaire was send to their homes. Patient characteristics, complications, and re-interventions were retracted from the medical charts. Patients who revisited the hospital underwent a face-to-face interview with an independent investigator at the hospital to obtain more information on complications. Physical examination was performed to detect possible exposure of the bulk material and assess the objective cure by means of a standardized cough stress test (CST). Physical

examination was performed by the treating doctor, but in presence of an independent investigator, to limit bias.

Outcomes

The primary outcome was patients' satisfaction which was determined by three questions from the validated surgical satisfaction questionnaire (SSQ-8)[15]: "How satisfied are you with the results for your surgery?," "Looking back, if you had to do it all over again, would you have the surgery again?," and "Would you recommend this surgery to someone else?." Answers of the SSQ questions consisted of a 5-point Likert scale ranging from "very satisfied" to "very unsatisfied" or from "yes" to "never." Patients' satisfaction was defined if answers corresponded with "very satisfied" and "satisfied" or "yes" and "maybe." Secondary outcomes were: subjective cure, objective cure, severity of SUI symptoms, complications and re-interventions, and disease-specific QoL. Subjective cure was assessed by the patients global impression of improvement (PGI-I).[16]

The PGI-I is a validated question to determine the patients improvement of symptoms compared with how it was before the treatment. Answers ranges from "very much better" to "very much worse." We defined patients "subjectively cured" if answers corresponded with: "very much better" or "much better." Objective cure was defined as a negative standardized CST. The CST was performed in lithotomy position with a minimum of 250 mL in the bladder. The Sandvik severity scale (two questions that corresponds with the amount and frequency of UI) and patients global impression of severity (PGI-S) were used to assess the severity of SUI symptoms.[17]

Complications were determined by a face- to-face interview and from medical charts. Urinary tract infections (UTI) within 6 weeks after treatment were scored as a complication. Re-intervention was defined as any surgical intervention after bulk injection therapy Urolastic to treat recurrent, persistent SUI symptoms or complications. This implied: reinjection of Urolastic, excision of bulk material, suburethral sling surgery or other (surgical) treatments for SUI. The following disease- specific QoL questionnaires were used: International Consultation on Incontinence Questionnaire (ICIQ-short form),[18] Incontinence Impact Questionnaire short form (IIQ-7), and Urogenital Distress Inventory short form (UDI-6).[19]

Patients' satisfaction, subjective cure and objective cure were presented as the time-after-treatment, according to the following time frames: 0 to 12 months, 13 to 24 months, and ≥25 months post-treatment.

Statistical analysis

Demographic and baseline characteristics were summarized using standard descriptive methods. Nominal and ordinal data were described using frequencies and percentages. Normally distributed continuous data were described using mean and standard deviation.

All used questionnaires were calculated as proposed by the composers. $\chi 2$ and Mann-Whitney U were used for categorical data and linear data, respectively. A $P < .05$ was considered statistically significant. Statistical analysis has been performed using IBM SPSS Statistics 24.

Results

Eligible patients treated between May 2014 and July 2018 were invited to participate. Figure 1 presents the flowchart of the enrolment. Table 1 shows the patient's and procedural characteristics of the 110 patients and symptom scores based on completed questionnaires (n = 87). The mean age was 64 years. The median time-after- treatment for hospital revisit was 25 months (interquartile range: 14;35 months, range, 1-58 months). Appendix 1 shows overall outcomes and outcomes per study site.

Figure 1. Flowchart patient recruitment

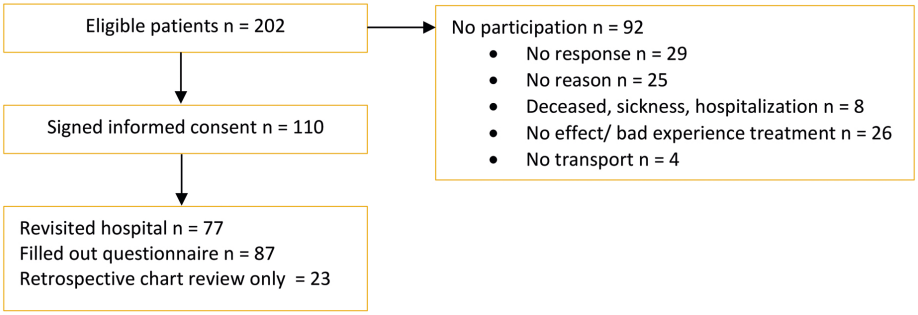


Table 1. Patient and procedural characteristics

	Total 110	
	N	%
Age *mean* (SD)	64 (13)	
BMI *mean* (SD)	27 (5)	
Parity *median* (IQR)	2 (2-3)	
Smoker at time of procedure	12	11
Postmenopausal	90	82
Type of urinary incontinence		
Stress urinary incontinence	51	46
Mixed urinary incontinence	59	59
Recurrent urinary tract infections		
Yes	24	22
No	58	53
Unknown	26	24

Table 1. Patient and procedural characteristics *(continued)*

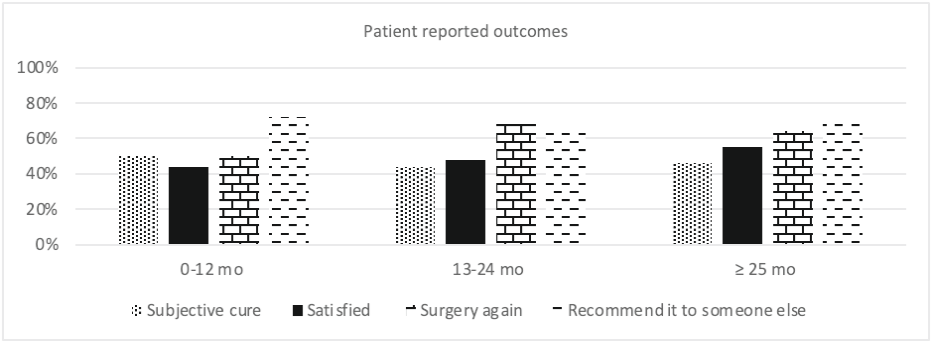
	Total 110	
	N	%
Preoperative pad use per day *mean* (SD)	3 (2)	
Sexually active (n) %	59	54
Previous treatment for SUI[a]		
No treatment	23	21
PFMT	45	41
Sub-urethral sling surgery (≥1)	29	26
Injection therapy bulking agent	5	5
Burch colposuspension	5	3
Other [b]	10	9
Unknown	2	2
Indication for Urolastic treatment		
Preference patient/physician	67	61
After failed surgery	42	38
Contra-indication anesthesia	1	1
Amount (cc) of injected bulk material per location in median (range)		
2 o'clock	1 (0.4-1.2)	
5 o'clock	1 (0.0-1.2)	
7 o'clock	1 (0.0-1.2)	
10 o'clock	0.8 (0.0-1.2)	
	N = 87	
Time-after-treatment median (IQR)	25 (14;35)	
months	18	21
13-24 months	25	29
>24 months	44	51
Frequency of urinary incontinence before Urolastic treatment		
Less than one time a month	2	2
Once or a few times a week	16	18
Every day/night	68	78
Amount of urinary incontinence before Urolastic treatment % (n)		
Droplets	10	11
More than droplets	76	87

[a] Total number is n=119, due to the fact that some patients have had multiple therapies. [b] Other: Anterior colporrhaphy (n=4), laser (n=2), myoblasts injection (n=2), pessary (n=1), estrogen (n=1)
Abbreviations: BMI, body mass index; IQR interquartile range; SD, standard deviation; SUI, stress-urinary incontinence.

Patients' satisfaction and subjective cure

Patients' satisfaction was 51%. Sixty-two percent of the patients would have PDMS-U again and 69% would have recommended PDMS-U to someone else. The subjective cure was 46%. Subjective outcomes following time-after- treatment time frames did not significantly differ (Figure 2).

Figure 2. Patient's satisfaction and subjective cure following time-after-treatment



Subjective cure is defined as: answers corresponding to 'very much better' or 'much better' on the Patient Global Impression of Improvement (PGI-I). Satisfied is defined as: answers corresponding to 'very satisfied' or 'satisfied' on the surgical satisfaction questionnaire (SSQ-8). Surgery again is defined as: answers corresponding to 'yes' and 'maybe (probably yes)' on the SSQ-8. Recommend it to someone else is defined as: answers corresponding to 'yes' and 'maybe (probably yes)' on the SSQ-8.

Objective cure

The CST was examined in 74 patients and overall 47% (n = 35) were objectively cured. The objective cure decreased significantly following the time-frames 0 to 12, 13 to 24, and more than or equal to 25 months: 77%, 56%, and 35% (P = .02).

Severity of SUI symptoms

Overall 85% (n = 74) still experienced symptoms of SUI after PDMS-U treatment; 53% experienced SUI symptoms every day/night and 49% experienced urine leakage "more than droplets." Incontinence material for SUI symptoms after PDMS-U was used in 47%.

Forty-six percent (n = 40) found the remaining form of UI acceptable, while 17% (n = 15) scored their symptoms of SUI "severe" on the PGI-S.

Complications and re-interventions

Per-procedural complications did not occur. Table 2 represents the post-procedural complications and re-interventions.

Overall, 60% (n = 66) encountered postoperative complications. Most prevalent complications were: urinary retention (22%), pain (15%), dyspareunia (15%), and experience of an uncomfortable hard feeling in the vagina (15%).

Urinary retention was treated with a catheter-a-demeure or clean intermittent catheterization for a median duration of 4 days. One patient needed excision of the bulk material, 7 days after the procedure to resolve the retention.

Eight patients had exposure of bulk material through the vaginal wall. Seven patients were treated with excision of bulk material, in one patient, the treatment of the exposure was unknown. None of the patients with exposure showed signs of infection. Hair-like strands of bulk material coming out of the injection site was observed in 13 patients (noticed mostly during the revisit), however, this adverse event was not counted as a complication, as this was a common part of the procedure and did not need any further treatment or were easily removed by tweezers.

Erosion of the bulk material to the urethra (n = 2), to the bladder (n = 2), or elsewhere under the vaginal wall (n = 2) occurred in six patients. Urethral erosion caused local pain, but could easily be removed by urethroscope. Patients with bladder erosion complained of pain, recurrent UTI's or haematuria. Both patients were free of complaints after removal of the bulk material by cystoscopic approach.

Patients with erosion under the vaginal wall showed a thin epithelial layer and were treated with local estrogen, later excision of the bulk material was still indicated. One patient had a small vaginal abscess 4 days after Urolastic treatment, which was treated with antibiotics, followed by excision 2 months later.

Other complications were: UTI (n = 8), urgency de novo (n = 7), spontaneous loss of bulk material (n = 3), hematoma (n = 1), and haematuria (n = 1). Prevalence of re-intervention including re-injection, excision, or other re-interventions was 33% (n = 36).

Re-injection of PDMS-U was done in seven patients (6%). Median time-after-treatment of re-injection was 4 months (range: 0 days to 18 months). In three patients, the re-injection was performed directly after the initial procedure. Five of the seven patients that had undergone re-injection revisited the hospital. At the study visit, four out of five were not subjective and objectively cured and all five patients were unsatisfied with the results.

Excision of bulk material was indicated in 18% (n = 20). Median time-after-treatment to excision was 10 months (range: 7 days to 26 months). Reasons for excision were: pain other than dyspareunia (n = 9), exposure (n = 7), erosion (n = 6), persistent SUI (n = 3), dyspareunia (n = 2), recurrent UTI (n = 1), and urinary retention (n = 1). Forty-five percent (n = 9) of the excisions were done under local analgesia and 55% (n = 11) were done under general or spinal anaesthesia.

Table 2. Complications and re-interventions

Adverse events	Total 110	
	N	%
Urinary retention	24	21.8
CAD for < 48 hours	7	29.2
CAD for ≥ 48 hours	13	54.2
Unknown	3	12.5
Pain[a]	16	14.5
Dyspareunia	16	14.5
Uncomfortable hard feeling vagina[b]	16	14.5
Urinary tract infection	10	9.1
Exposure (through vaginal wall)	8	7.3
Urgency incontinence de novo	7	6.4
Erosion (through urethra or bladder)	6	5.4
Spontaneous loss bulk material	3	2.7
Infection at injection site	1	0.9
Hematuria	1	0.9
Hematoma at injection site	1	0.9
Re-interventions		
Excision of Urolastic®	20	18.1
2 O'clock location	4	20
5 O'clock location	8	40
7 O' clock location	11	55
10 O'clock location	5	25
Unknown location	1	0.5
Other location[c]	5	25
Re-injection	7	6.3
MUS-operation after Urolastic treatment	6	5.5
Other re-intervention[d]	3	2.7

Note: Overview of complications and reinterventions.
[a]Pain urogenital area >2 wk after treatment, other than dyspareunia.
[b]An uncomfortable feeling of the presence of bulk material during daily activities without pain.
[c]Other location of excision: bladder (n = 2), para-urethral left (n = 2), para-urethral left, and right (n = 1).
[d]Rectus fascia sling (n = 1), PFMT (n = 1), and excision hematoma (n = 1).
Abbreviations: CAD, catheter a demeure; MUS, mid-urethral sling; PFMT, pelvic floor muscle training

Quality of life

Table 3 shows the scores of disease-specific QoL questionnaires related to the PGI-I. A significant better QoL of UDI-6, IIQ-7, and ICIQ-SF was found in patients with improved symptoms (P < .01).

Table 3. Disease-specific quality of life

	Improved	Similar	Worsened	p-value
UDI-6 Total *mean* (SD)	29.2 ± 18.7	44.1 ± 17.7	52.3 ± 25.1	<0.01
Irritative subscale	31.1 ± 28.5	46.0 ± 26.8	60.3 ± 30.1	<0.01
Stress subscale	38.8 ± 26.6	54.9 ± 27.5	65.3 ± 29.7	<0.01
Obstructive subscale	18.3 ± 19.1	31.4 ± 35.3	37.2 ± 28.8	0.17
IIQ-7 Total *mean* (SD)	22.6 ± 22.1	40.1 ± 29.0	47.9 ± 29.9	<0.01
Physical activity	23.9 ± 22.8	35.4 ± 34.9	50.0 ± 31.8	0.03
Mobility	22.1 ± 26.1	39.6 ± 35.9	46.2 ± 36.1	0.03
Social function	25.2 ± 31.9	41.2 ± 38.2	53.8 ± 34.8	0.02
Emotional health	18.6 ± 23.5	39.2 ± 38.6	53.8 ± 32.7	<0.01
ICIQ-SF Total *mean* (SD)	9.2 ± 4.5	15.4 ± 4.2	15.9 ± 4.9	<0.01

Disease-specific quality of life related to improved, similar or worsened outcome on the Patient Global Impression of Improvement (PGI-I) scale.
Abbreviations: ICIQ-SF, International Consultation on Incontinence Questionnaire Short Form; IIQ-7, Incontinence Impact Questionnaire; SD, standard deviation; UDI-6, Urogenital Distress Inventory.

Subgroup analysis

Appendix 2, an overview of subgroup analysis on patient characteristics, showed that clinical success and satisfaction was not influenced by patient's age or body mass index. Patients who have had previous surgery before PDMS-U were more likely to be objectively cured compared with patients with no prior or only conservative treatment (61% vs 37%; P = .04). Patients undergoing PDMS-U as secondary intervention did not encounter more complications (61% vs 58%; P = .69).

Regarding the physicians learning curve, patients of the first 20 procedures were more likely to be satisfied compared with the patients more than 20 procedures (75% vs 41%; P = < .01). No statistically significant differences were found regarding the procedure number and complication rate (66% vs 57% P = .40), nor for subjective cure or objective cure. Analysis on site dependent outcomes showed that only site 2 had higher objective cure rates compared with site 3 (odds ratio, 8.69; P < .01).

Discussion

In this study, we primarily evaluated the patients' satisfaction being treated with PDMS-U for SUI. Second, we assessed the subjective cure, objective cure, severity of symptoms, complications, and re-intervention rate and disease-specific QoL.

Although 85% of the patients still experienced symptoms of SUI after a median period of 25 months, 51% were satisfied with the results and 69% would recommend the treatment to someone else. The patients' satisfaction and subjective cure remained stable during time-after-treatment up to more than or equal to 25 months, whereas objective cure significantly worsened over time. Although reinjection of PDMS-U is a common option to improve outcomes, this was only done in 6% and the outcomes did not improve. Urinary retention, pain, and dyspareunia were the most prevalent complications. Excision of bulk material to treat severe or persistent complications such as pain, exposure or erosion was indicated in 18%.

Our study shows that almost half of the patients were satisfied after PDMS-U, 34% were not. The high number of SUI symptoms after treatment (85%), relative high chance to encounter complications (60%), and undergo a re-intervention (33%) can contribute to dissatisfaction.

The results on subjective and objective cure are comparable with other studies regarding PDMS-U. Kowalik et al[8] included patients with complicated SUI with a poor expected outcome and reported a subjective cure rate of 56% at 6 months follow-up. Another study performed a telephonic survey among patients treated with Urolastic for regular care in a general hospital and tertiary referral hospital. The subjective cure of the general hospital with a median follow-up time of 12 months was higher (61% vs 50%), but the subjective cure of the tertiary referral hospital after a median follow-up of 25 months was similar (43% vs 46%).[20]

The objective cure, also assessed by the CST, showed a similar decreasing trend corresponding with time-after-treatment of 6 months, 12 months, and 24 months follow-up (65%, 59%, and 33%).[8, 9, 12]

In conclusion, patients can be satisfied while having persistent symptoms of SUI. Bulk injection therapy is known for the attractive safety profile, with having fewer complications as compared with open surgery.[6, 7] Complications occur in one out of three patients and are mostly transient without requiring surgical treatment.[21] Our study shows a higher risk of complications (60% vs 24%) and higher number of re-interventions (18% vs 11%) compared with PDMS-U outcomes reported in a systematic review.[14]

This could be due to the fact that the follow-up in our study was longer so the chance on a complication was higher. To improve the acceptance of PDMS-U for patients, future studies can look into options to lower the number of operative re-interventions, for example, inject a lower amount bulk material, determine the ideal position of the bulk material, and if necessary adapt the injection device to achieve this. For example, although we reported patients with "erosion," it is not certain whether migration of the bulk material resulted in erosion or that the bulk material was initially injected too superficial under the epithelial layer or in the urethra or bladder.

In this study, we have evaluated the learning curve of the physician. Subgroup analysis remarkably showed that patients of procedure number 0 to 20 were more satisfied with results than patients of procedure number more than 20, while objective cure or complication rate did not differ. Because in general physicians learn a procedure, beginning with the most complicated patients that already have undergone multiple treatments, it could be that these patients were more easily satisfied.

This study has several limitations. First, inherent to the nature of a cross-sectional design, some patients were not willing to participate or did not respond. Hence, it is uncertain whether our findings are representative for the whole population of women indicated for a bulking agent.

Second, lack of preoperative data is a major limitation that could have affected the interpretation of outcomes. Missing information on micturition status or inaccurate recall by the patient made it uncertain to what extent symptoms have improved.

Third, the retrospective data collection from medical charts could be insufficient, especially complications may have been under-reported.

Fourth, one should be careful to interpret the outcomes of the objective cure, because the baseline measurements were not available.

Finally, one could argue that validated questionnaires such as the ICIQ-SF have no additional value when assessed only after surgery. However, a strong correlation between PGI-I and ICIQ-SF as well as validation of a cut-off score of the ICIQ-SF postoperatively have been reported.[22]

The European Union medical device regulation has set several goals regarding legislation, among other to strengthening post-marketing surveillance and risk evaluation.[23]

PDMS-U has been in the market for several years and although cohort studies have been performed, no study has evaluated this product for over 2 years follow-up, like we did. This is the first study that also evaluated patients' satisfaction and long-term safety

assessment of PDMS-U. As we obtained data from standard care, the results are generalizable and useful to counsel patients about satisfaction and safety of SUI treatment with PDMS-U.

Conclusion

About half of the patients being treated with PDMS-U were satisfied and subjectively cured 2 years after treatment, although the majority still experienced symptoms of SUI. Most complications were mild and transient, however, in 18% excision bulk material was indicated for severe or persistent complications such as pain, exposure, or erosion.

Appendix 1. Overview outcomes per site

	Overall	Site 1	Site 2	Site 3	Site 4
Patient characteristics					
Eligible patients	202	65	64	57	16
Included patients	110	25	36	40	9
Filled out questionnaire	87	25	36	24	2
Age *mean* (SD)	64±13	61±10.6	64±12	63±14.4	77.4±6.3
No surgery before PDMS-U n (%)	70 (64)	11 (44)	10 (27.8)	37 (92.5)	9 (100)
With surgery before PDMS-U n (%)	40 (36)	14 (56)	26 (69.4)	3 (7.5)	0 (0)
Mixed urinary incontinence n (%)	59 (54)	10 (0.4)	22 (61.1)	19 (47.5)	8 (88.9)
Procedural characteristics					
Amount (cc) of injected bulk material per location in median (range)					
2 O'clock	1.0 (0.4-1.2)	0.8 (0.6-0.8)	1.0 (0.8-1.2)	1.0 (0.4-1.0)	1.0 (0.8-1.0)
5 O'clock	1.0 (0.0-1.2)	1.0 (0.8-1.2)	1.0 (0.0-1.2)	0.8 (0.4-1.0)	1.0 (0.8-1.0)
7 O'clock	1.0 (0.0-1.2)	1.0 (0.8-1.2)	1.0 (0.0-1.2)	0.8 (0.4-1.0)	1.0 (0.0-1.0)
10 O'clock	0.8 (0.0-1.2)	0.8 (0.6-0.8)	1.0 (0.8-1.2)	1.0 (0.4-1.0)	0.8 (0.0-1.0)
Time-after-treatment median (IQR)	25 (14;35)	34 (25;38)	13 (7;18)	33 (28;40)	31 (34;-)
0-12 mo n (%)	21 (18)	0 (0)	17 (47)	1 (4.2)	0 (0)
13-24 mo n (%)	29 (25)	4 (16)	19 (53)	2 (8.3)	0 (0)
>24 mo n (%)	51 (44)	21 (84)	0 (0)	21 (87.5)	2 (100)

	Overall	Site 1	Site 2	Site 3	Site 4
Site and physician characteristics					
Type of hospital		Academic hospital	General hospital	General hospital	Teaching hospital
Profession physician		Gynaecologist	Urologist	Urologist	Urologist
Total performed Urolastic procedures		67	67	57	23
Outcomes					
SSQ-8: "*How satisfied are you with the results for your surgery?*" n (%)					
Very satisfied	22 (25.3)	6 (24)	10 (27.7)	5 (20.8)	1 (50)
Satisfied	22 (25.3)	4 (16)	10 (27.7)	8 (33.3)	0 (0)
Neutral	13 (14.9)	3 (12)	7 (19.4)	3 (12.5)	0 (0)
Unsatisfied	24 (27.6)	9 (36)	8 (22.2)	6 (25)	1 (50)
Very unsatisfied	6 (6.9)	3 (12)	1 (2.7)	2 (8.3)	0 (0)
Satisfaction rate n (%)	44 (51)	10 (40)	20 (55.6)	13 (54.2)	1 (50)
SSQ-8: "*Looking back, if you had to do it all over again, would you have the surgery again?*" n (%)					
Yes	46 (52.9)	12 (48)	22 (61.1)	11 (45.8)	1 (50)
Maybe	8 (9.2)	1 (4)	2 (5.5)	5 (20.8)	0 (0)
Unsure	8 (9.2)	1 (4)	5 (13.8)	2 (8.3)	0 (0)
I don't think so	15 (17.2)	5 (20)	6 (16.6)	3 (12.5)	1 (50)
Never	10 (11.5)	6 (24)	1 (2.7)	3 (12.5)	0 (0)
SSQ-8: "*Would you recommend this surgery to someone else?*" n (%)					
Yes	51 (58.6)	11 (44)	23 (63.8)	16 (66.7)	1 (50)
Maybe	9 (10.3)	2 (8)	4 (11.1)	3 (12.5)	0 (0)
Unsure	13 (14.9)	6 (24)	6 (16.6)	1 (4.1)	0 (0)
I don't think so	8 (9.2)	3 (12)	2 (5.5)	2 (8.3)	1 (50)
Never	6 (6.9)	3 (12)	1 (2.7)	2 (8.3)	0 (0)

	Overall	Site 1	Site 2	Site 3	Site 4
Patient global impression of improvement (PGI-I) n (%)					
Very much better	22 (25.3)	4 (16)	12 (33.3)	6 (25)	0 (0)
Much better	18 (20.7)	3 (12)	8 (22.2)	6 (25)	1 (50)
A little better	17 (19.5)	5 (20)	6 (16.6)	6 (25)	0 (0)
No change	17 (19.5)	7 (28)	7 (19.4)	3 (12.5)	0 (0)
A little worse	3 (3.4)	1 (4)	1 (2.8)	0 (0)	1 (50)
Much worse	6 (6.9)	3 (12)	2 (5.5)	1 (4.2)	0 (0)
Very much worse	4 (4.6)	2 (8)	0 (0)	2 (8.3)	0 (0)
Subjective cure n (%)	40 (46)	7 (28)	20 (55.6)	12 (50)	1 (50)
Still have symptoms of stress urinary incontinence (%)	74 (85)	24 (96)	30 (83)	18 (74)	2 (100)
Sandvik severity scale: frequency of urinary incontinence n (%)					
Less than one time a month	4 (4.6)	1 (4)	3 (8.3)	0 (0)	0 (0)
Once or a few times a month	11 (12.6)	5 (20)	4 (11.1)	2 (8.3)	0 (0)
Once or a few times a week	15 (17.2)	6 (24)	5 (13.8)	4 (16.7)	0 (0)
Every day/night	46 (52.9)	13 (52)	20 (55.5)	11 (45.8)	2
Amount of urinary incontinence n (%)					
Droplets	32 (36.8)	13 (52)	13 (36.1)	6 (25)	0 (0)
More than droplets	43 (49.4)	12 (48)	17 (47.2)	12 (50)	2 (100)
Patient global impression of severity (PGI-S) n (%)					
Not applicable, I don't have voiding problems		0 (0)	13 (36.1)	1 (4.2)	0 (0)
Normal	5 (5.7)	9 (36)	3 (8.3)	11 (45.8)	1 (50)
Mild	24 (27.6)	11 (44)	12 (33.3)	5 (20.8)	1 (50)
Moderate	29 (33.3)	4 (16)	7 (19.4)	4 (16.7)	0 (0)
Severe	15 (17.2)	1 (4)	1 (2.7)	3 (12.5)	0 (0)
Objective cure n (%)	35/74 (47.3)	8/25 (32)	19/24 (79.2)	7/23 (30.4)	1/2 (50)

	Overall	Site 1	Site 2	Site 3	Site 4
Complications and reinterventions n (%)					
Urinary retention	24 (21.8)	1 (4)	10 (27.7)	8 (20)	5 (56)
Pain	16 (14.5)	5 (20)	3 (8.3)	4 (10)	4 (44)
Dyspareunia	16 (14.5)	7 (28)	4 (11.1)	5 (12.5)	0 (0)
Uncomfortable hard feeling	16 (14.5)	5 (20)	5 (13.8)	4 (10)	2 (22)
Urinary tract infection	10 (9.1)	0 (0)	6 (16.6)	2 (5)	2 (22)
Urgency de novo	7 (6.4)	3 (12)	0 (0)	4 (10)	0 (0)
Exposure	8 (7.3)	2 (8)	3 (8.3)	1 (2.5)	2 (22)
Erosion	6 (5.4)	2 (8)	0 (0)	2 (5)	2 (22)
Reinjection	7 (6.3)	1 (4)	0 (0)	3 (7.5)	3 (33)
Excision	20 (18.1)	6 (24)	4 (11.1)	6 (15)	4 (44)
ICIQ-SF-score mean (SD)	11.5±5.4	12.9±5.2	10.6±5.6	11.1±5.6	13±2.8
IIQ-SF-score mean (SD)	30.0±26.6	39.0±29.7	25.0±23.5	25.9±26.5	37.5±11.8
UDI-SF-score mean (SD)	35.7±21.4	43.3±22.8	31.3±18.9	32.4±21.1	47.2±27.5

Note: Total overview of outcomes per study site: patients' satisfaction, PGI-I, Sandvik severity scale, PGI-S, objective cure, complications, reinterventions, and quality of life.

Abbreviations: ICIQ, International Consultation on Incontinence Questionnaire Short Form; IIQ, Incontinence Impact Questionnaire Short Form; IQR, interquartile range; PDMS-U, polydimethylsiloxane-Urolastic; PGI-I, patients global impression of improvement; PGI-S, patients global impression of severity; SD, standard deviation; SSQ-8, Surgical Satisfaction Questionnaire; UDI, Urogenital Distress Inventory Short Form.

Appendix 2.

	Objective cure		Subjective cure		Satisfied	
Subanalysis for patient characteristics						
Age, continuous†		0.34		0.92		0.11
Age (median, IQR)	66.0 (60.0-74.0)		64.0 (56.8-70.8)		66.5 (59.5-72.0)	
Age, categorical (p)ᵛ		0.12		0.74		0.29
Lowest-50 (n,%)ǂ	3 (33.3)		5 (38.5)		4 (38.8)	
50-75 (n,%)ǂ	25 (44.6)		31 (38.4)		34 (39.1)	
>75-highest (n,%)ǂ	7 (77.8)		4 (40.0)		6 (60.0)	
BMI, continuous†		0.51		0.81		0.71
Age (median, IQR)	26.9 (24.2-29.4)		26.5 (24.4-30.1)		27.2 (24.4-30.1)	
BMI, categorical (p)ᵛ		0.53		0.97		0.59
0-25 (n,%)ǂ	11 (52.4)		12 (46.2)		12 (46.2)	
>25 (n,%)ǂ	23 (44.2)		27 (45.8)		31 (52.5)	
MUI vs. SUI (p)ᵛ		0.80		0.62		0.59
MUI (n,%)ǂ	19 (48.7)		20 (43.5)		22 (47.8)	
SUI (n,%)ǂ	16 (45.7)		20 (48.8)		22 (53.7)	
No surgery before PDMS-U vs with surgery before PDMS-U (p)ᵛ		0.04		0.27		0.44
No surgery before PDMS-U (n,%)ǂ	16 (37.2)		20 (40.8)		23 (46.9)	
With surgery before PDMS-U (n,%)ǂ	19 (61.3)		20 (52.6)		21 (55.3)	

	Objective cure		Subjective cure		Satisfied	
Subanalyses for procedural characteristics						
Procedure 1-20 vs. >20 (p)ɣ		0.42		0.06		<0.01
1-20 (n,%)ǂ	12 (54.5)		15 (62.5)		18 (75)	
>20 (n,%)ǂ	23 (44.2)		25 (39.7)		26 (41.3)	
Subanalyses per centre						
Centre (p)ɣ		<0.01		0.19		0.66
1 (n,%)ǂ	8 (32)		7 (28)		10 (40)	
2 (n,%)ǂ	19 (79.2)		20 (55.6)		20 (55.6)	
3 (n,%)ǂ	7 (30.4)		12 (50)		13 (54.2)	
4 (n,%)ǂ	1 (50)		1 (50)		1 (50)	

Total overview of outcomes per study site: objective cure, subjective cure and satisfaction.

[1] Site 1: Academic Hospital;[2] Site 2: General Hospital; [3] Site 3: General Hospital;[4] Site 4: Teaching Hospital

† Mann Whitney U

ɣ Chi-square

ǂ Percentages presented as within categorical group

^Continuous variable

References

1 C. H. van der Vaart, J. R. de Leeuw, J. P. Roovers & A. P. Heintz. *The effect of urinary incontinence and overactive bladder symptoms on quality of life in young women*. BJU Int 2002;90(6):544-9.

2 C. H. van der Vaart, J. R. de Leeuw, J. P. Roovers & A. P. Heintz. *[The influence of urinary incontinence on quality of life of community-dwelling, 45-70 year old Dutch women]*. Ned Tijdschr Geneeskd 2000;144(19):894-7.

3 Y. S. Hannestad, G. Rortveit, H. Sandvik, S. Hunskaar & E. s. E. o. I. i. t. C. o. N.-T. Norwegian. *A community-based epidemiological survey of female urinary incontinence: the Norwegian EPINCONT study. Epidemiology of Incontinence in the County of Nord-Trondelag*. J Clin Epidemiol 2000;53(11):1150-7.

4 C. R. Chapple, F. Cruz, X. Deffieux, A. L. Milani, S. Arlandis, et al. *Consensus Statement of the European Urology Association and the European Urogynaecological Association on the Use of Implanted Materials for Treating Pelvic Organ Prolapse and Stress Urinary Incontinence*. Eur Urol 2017;72(3):424-31.

5 A. M. de Vries, P. L. Venema & J. Heesakkers. *Midurethral support is also necessary for reflex closure of the urethra*. Neurourol Urodyn 2018;37(8):2965-72.

6 V. Kirchin, T. Page, P. E. Keegan, K. O. Atiemo, J. D. Cody, et al. *Urethral injection therapy for urinary incontinence in women*. Cochrane Database Syst Rev 2017;7:CD003881.

7 A. M. Itkonen Freitas, M. Mentula, P. Rahkola-Soisalo, S. Tulokas & T. S. Mikkola. *Tension-Free Vaginal Tape Surgery versus Polyacrylamide Hydrogel Injection for Primary Stress Urinary Incontinence: A Randomized Clinical Trial*. J Urol 2020;203(2):372-78.

8 C. R. Kowalik, F. M. Casteleijn, H. W. F. van Eijndhoven, S. E. Zwolsman & J. W. R. Roovers. *Results of an innovative bulking agent in patients with stress urinary incontinence who are not optimal candidates for mid-urethral sling surgery*. Neurourol Urodyn 2018;37(1):339-45.

9 K. Futyma, P. Miotla, K. Galczynski, W. Baranowski, J. Doniec, et al. *An Open Multicenter Study of Clinical Efficacy and Safety of Urolastic, an Injectable Implant for the Treatment of Stress Urinary Incontinence: One-Year Observation*. Biomed Res Int 2015;2015:851823.

10 J. Zajda & F. Farag. *Urolastic-a new bulking agent for the treatment of women with stress urinary incontinence: outcome of 12 months follow up*. Adv Urol 2013;2013:724082.

11 J. Zajda & F. Farag. *Urolastic for the treatment of women with stress urinary incontinence: 24-month follow-up*. Cent European J Urol 2015;68(3):334-8.

12 K. Futyma, L. Nowakowski, K. Galczynski, P. Miotla & T. Rechberger. *Nonabsorbable urethral bulking agent - clinical effectiveness and late complications rates in the treatment of recurrent stress urinary incontinence after 2 years of follow-up*. Eur J Obstet Gynecol Reprod Biol 2016;207:68-72.

13 Z. A. Siddiqui, H. Abboudi, R. Crawford & S. Shah. *Intraurethral bulking agents for the management of female stress urinary incontinence: a systematic review*. Int Urogynecol J 2017;28(9):1275-84.

14 A. M. de Vries, H. Wadhwa, J. Huang, F. Farag, J. Heesakkers, et al. *Complications of Urethral Bulking Agents for Stress Urinary Incontinence: An Extensive Review Including Case Reports*. Female Pelvic Med Reconstr Surg 2018;24(6):392-98.

15 S. J. Haff RE, Lucente VR, Murphy M. *The surgical satisfaction questionnaire (SSQ-8): a validated tool for assessment of patient satisfaction following surgery to correct prolapse and/or incontinence.".* Journal of minimal Invasive Gynecology 2011;18.6:S49-S50.

16 I. Yalcin & R. C. Bump. *Validation of two global impression questionnaires for incontinence*. Am J Obstet Gynecol 2003;189(1):98-101.

17 H. Sandvik, S. Hunskaar, A. Seim, R. Hermstad, A. Vanvik, et al. *Validation of a severity index in female urinary incontinence and its implementation in an epidemiological survey.* J Epidemiol Community Health 1993;47(6):497-9.

18 A. Klovning, K. Avery, H. Sandvik & S. Hunskaar. *Comparison of two questionnaires for assessing the severity of urinary incontinence: The ICIQ-UI SF versus the incontinence severity index*. Neurourol Urodyn 2009;28(5):411-5.

19 J. S. Uebersax, J. F. Wyman, S. A. Shumaker, D. K. McClish & J. A. Fantl. *Short forms to assess life quality and symptom distress for urinary incontinence in women: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program for Women Research Group*. Neurourol.Urodyn. 1995;14(2):131-39.

20 A. M. de Vries, H. M. K. van Breda, J. G. Fernandes, P. L. Venema & J. Heesakkers. *Para-Urethral Injections with Urolastic(R) for Treatment of Female Stress Urinary Incontinence: Subjective Improvement and Safety.* Urol Int 2017;99(1):91-97.

21 E. Kocjancic, S. Mourad & O. Acar. *Complications of urethral bulking therapy for female stress urinary incontinence*. Neurourology and Urodynamics 2019;38(S4):S12-S20.

22 D. Karmakar, A. Mostafa & M. Abdel-Fattah. *A new validated score for detecting patient-reported success on postoperative ICIQ-SF: a novel two-stage analysis from two large RCT cohorts*. Int Urogynecol J 2017;28(1):95-100.

23. In: C. o. t. E. U. EP., ed. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC Publications Office of the European Union., 2017.

Chapter 8

General Discussion

Background

Medicine is a field of science that is continuously evolving to try to improve health care.

The development of new treatment techniques is an example of this evolvement. Innovative techniques have the potency to - and are intended to - improve patient related and treatment outcomes, or to improve diagnostic accuracy. The drawback is that these techniques can cause potential harm, disappointing results or increased health care costs.[1]

The introduction of innovative techniques into clinical practice should be regulated, taking safety, effectiveness and costs into account. After introduction of an innovative intervention this intervention should be monitored in the short and the long term and outcomes of such evaluations should be used to improve clinical practice.[1]

In this thesis, we have evaluated the use of (PP) mesh in pelvic reconstructive surgery and polydimethylsiloxane Urolastic® (PDMS-U) bulking agent in urinary incontinence, two "innovative" techniques in the treatment of pelvic floor disorders. In this chapter, we will discuss the main findings of these evaluations and implications for clinical practice and further research.

Part one: The use of PP mesh in pelvic reconstructive surgery.

Introduction of PP mesh implants for pelvic reconstructive surgery.
Mesh implants for pelvic reconstructive surgery have been introduced in the mid 1990's under the US FDA 510 (k) system. This pre-market notification process simplifies the introduction of new products into the market.[2] To obtain approval for a medical device under this ruling, a product has to be substantially equivalent and at least as safe and effective as a product that already has been approved.[2] In the case of mesh for pelvic reconstructive surgery, approval was based on its similarity with meshes for hernia repair. No additional safety or efficacy studies were required with data on the vaginal mesh products. A widespread application of these meshes for urinary incontinence and pelvic organ prolapse followed worldwide.[2, 3]

Unfortunately, in the years following, complications unique to vaginal mesh products were encountered and hence restrictions for the use of mesh have been made. In 2008 the FDA issued a Public Health Notification (PHN) about mesh related complications and in 2011 they issued a safety communication, stating that mesh related complications are not rare and that there is a lack of evidence that vaginal mesh surgery is more effective than traditional repair.[4]

In 2016, the FDA reclassified the mesh products and pre-market approval to support safety and effectiveness became mandatory to obtain approval for market introduction.

Women that had suffered from mesh related complications started to sue the companies that marketed the transvaginal mesh products. They accused the mesh manufacturers of misleading the FDA, the medical community, the patients and public about the true safety and effectiveness of the mesh products. More than 108,000 lawsuits have been filed and 8 billion dollar of settlements have been paid by mesh manufacturers by 2019.[5]

Consequently, the industry withdrew and stopped making implants for SUI and POP and research and development into female pelvic health became of lesser interest for these companies. Additionally certain countries decided to advice against the use of mesh or ban (vaginal) mesh products.[6]

Other countries have regulated the mesh use in pelvic reconstructive surgery. The European Urology Association (EAU) and European Urogynaecological Association (EUGA) issued a consensus document describing which women might still benefit from mesh-augmented surgery.[7] National societies, like the Dutch Society of Gynaecology (NVOG) regulated the use of mesh implants in pelvic reconstructive surgery.[8]

All the concerns regarding mesh surgery and the negative reporting in the media resulted in scared patients that were reluctant to have a mesh implant. Many women that were indicated for pelvic reconstructive mesh surgery refrained from treatment, because of fear of having mesh-related complications.

For certain groups of patients, like women with recurrent prolapse, mesh surgery however is still indicated to prevent prolapse recurrence. To gain better understanding if these women can benefit from mesh implants and what the consequence of mesh-related complications for these women is, we posed the research questions concerning mesh implants described in the introduction.

Long-term complications of vaginal mesh implants and Hr-QoI in women after vaginal mesh surgery with and without a mesh complication.

We set out this thesis with a total recall of patients that have been treated with vaginal mesh implants, because of prolapse recurrence or as a primary procedure when women participated in a clinical study. We aimed to explore long-term complications and patient satisfaction about treatment outcome of vaginal mesh surgery for POP in our referral center.

The most common long-term complications were pain and mesh exposure. Twenty-three out of 188 (12%) women reported pain symptoms, however 14 women already had pain prior to the mesh surgery. Nine women (5%) developed pain after the mesh insertion

and in three women (2%) pain was persistent despite treatment. The median follow-up was 40 months (range 12-76 months) and the meshes implanted were Perigee™, Apogee™ and Elevate® Anterior and Elevate® Posterior. The majority of patients were satisfied with their treatment (86%), even though mesh related complications were not uncommon in our center.

Pain is an invalidating complication of pelvic reconstructive surgery. In mesh surgery, the causative factor has been attributed to the mesh-prosthesis. The theory being that pain can develop due to contracture of the tissue surrounding the mesh.[9] It is important, however, to keep in mind that pain can also develop after native tissue repair. Milani et al. reported no statistical significant differences in pain complaints between vaginal mesh and native tissue repair after 7 years of follow up.[10]

The other long-term complication in our recall was mesh exposure. In 26 women (14%), an exposure was diagnosed during the follow up. Eleven women (6%) had a symptomatic exposure that had been treated surgically.

The exposure rates in literature vary considerately (5-42%).[10, 11] This widespread difference can be attributed to several factors. The duration of follow up may influences the exposure rate. The median time of detection of an exposure was 2.8 years in the study of Dykes et al. with a range of 8.3 years.[12] In our study the median follow-up was 40 months (range 12-76 months). The population under study can also influence exposure rates, for example, when risk factors are more frequently present in the studied population. Risk factors for mesh exposure that have been identified are total tension-free vaginal mesh, the years of experience in prolapse repair, smoking and concomitant hysterectomy.[13,14]

The type of mesh is also an important factor. When the transvaginal mesh was introduced into to market, the mesh was heavier than the meshes that were developed later on. The heavyweight meshes have shown to cause a greater inflammatory response and a greater decline in mechanical properties of the vagina than the lightweight meshes.[15, 16] When comparing exposure rates, lightweight mesh causes significant less exposure than the heavyweight mesh.[12]

Since so many variables can influence treatment outcome, we encourage our colleagues to counsel patients based on their own results, since we are of opinion that these numbers give a better reflection of daily practice than results from studies with different patient and mesh characteristics. We have shown that such a total recall is feasible and now council patient based on our own data.

After ascertaining the rate and kind of the most important mesh-related complications in the long-term in our study population, we were interested in the impact of these complications on the quality of patients' lives. Not all complications are symptomatic

and we wondered if the effect of restoration of anatomy and improvement of pelvic floor function would differ between women with and without a mesh-related complication.

We observed that disease specific Hr-QoL, related to micturition, defecation and sexual functioning is comparable between women with and without mesh-related complications. This might be explained by the fact that pelvic floor functioning is mostly related to vaginal anatomy, which is optimized by pelvic floor surgery. This is in line with the study of Zhang et al. that performed an observational study among women undergoing transvaginal mesh repair. They found no significant impact of mesh exposure on patients' quality of life.[17] We found no statistical differences in total PISQ-scores between groups. This is in contrast with the study of Milani et al.: They report that the presence of a mesh exposure was independently associated with deterioration of PISQ-scores in their study.[18] A possible explanation for the conflicting results with our report might be the difference in mesh type. The group of Milani studied the outcome of the Prolift, which is a heavier mesh type than the mesh in our study. As mentioned above, lightweight mesh causes less fibrosis and contraction as compared to heavier weight mesh.[15]

The outcome of surgical interventions for mesh-related complications in pelvic reconstructive surgery.

When women present to their physician with mesh-related complications it is important to be able to counsel them about their treatment possibilities. Women seek guidance regarding their chances of successful recovery and possible complications.

Improvement

In this thesis, we show that 75% of women report improvement of symptoms after mesh revision surgery in a tertiary referral hospital with a median follow-up of 1.7 (IQR 1.1–2.4) years. The percentage of symptom relief varies in reports on mesh-revision surgery. The outcome of this thesis is consistent with the study of Warembourg et. al. They report a cure rate of 78% after surgical management.[19] This study is comparable, since it also reports on symptom relief after surgery in a tertiary referral center and has a long term follow up.

Complications

Patients have to be counselled that complications can occur during and after mesh revision surgery. In our population, eight out of 59 patients (14%) experienced a serious complication. These included bowel lesions, bladder lesions and excessive blood loss during or after the surgical procedure. All complications could be treated and all patients recovered from these complications.

Prolapse or stress-incontinence recurrence

When soliciting for mesh revision surgery, patients worry that after mesh resection their POP or SUI will recur. In our population, overall POP recurrence in any compartment was

seen in 18 women (31%). POP recurrence in the specific compartment where the mesh had been removed was most common in the anterior compartment and seen in 5 women (8%).

In MUS revision, one third of women had SUI recurrence. Data could only be collected in six patients and should therefore be interpreted with care.

Other studies reporting on recurrent SUI after tape revision show that 14–23% of women have surgery for recurrent SUI and 49% have SUI recurrence.[20-22]

Multiple operations
Patients considering mesh revision surgery should be informed that they have a chance of 29% to be indicated for additional surgery after the mesh revision. Reasons for a re-intervention are persistent mesh complications, POP recurrence or SUI.

Surgical approach
The most frequent indication for mesh revision were pain symptoms, which were reported in 78% of patients in our study. The surgical approach to revise mesh-related complications was dependent of the kind of mesh-related symptom (exposure or pain or both) and of the mesh type and route of insertion. Most approaches were performed vaginally. We did not find any relation with the improvement of symptoms and the occurrence of serious adverse events related to the type of intervention.

An interesting point to discuss is whether mesh should be resected totally or partially. In the cross-sectional study that we performed for this thesis, the extent of mesh removal was dependent of the severity of symptoms, the location of tension/ fibrosis and risk of complications due to the proximity of visceral organs. In most patients, mesh remnants were left in situ with a positive outcome on symptom relief. Wolff et al. performed a review discussing whether total mesh removal is mandatory. They conclude that there are no high quality studies that clearly show that total mesh removal is more likely to result in pain reduction.[23] However this could be different in the light of alleged systemic complaints following mesh prosthesis insertion.

Polypropylene implants and the development of a systemic inflammatory response or autoimmune disease.
On consumer websites and discussion platforms the speculation has arisen that PP mesh implants can elicit a systemic inflammatory response causing a multitude of systemic complaints. If there would be prove of a causal relation between PP mesh and a systemic inflammatory response, total mesh removal would seem mandatory to achieve symptom relieve. However, total mesh removal is complex and total mesh removal may increase the risk of complications.

We performed a systematic review to gather the best available scientific evidence regarding the possible association between PP implants for inguinal hernia, ventral hernia or pelvic floor surgery and the development of systemic autoimmune syndromes. We found only four clinical studies regarding this topic.[24-27] We concluded that there is insufficient evidence to conclude that a causal association between PP mesh implants and the development of autoimmune syndromes exist.

However, these results should be interpreted with caution, since only retrospective studies were available and analysed.

Implication for daily practice and future perspective

In daily practice, women are often referred to their gynaecologists, because of prolapse recurrence. Treatment options for these patients are either conservative treatment, redo surgery with native tissue or implantation of a mesh prosthesis. The latter is the most effective treatment modality in these women, but women are scared regarding the possible detrimental effects of having a mesh-implant.

This thesis has been performed to be of aid in counselling women facing the choice of having redo surgery with native tissue or mesh surgery.

Women can be informed that although they have the risk of mesh-specific complications, most women are satisfied with treatment. The most frequent mesh related complications are pain or exposure. Mesh -related complications do not seem to influence health-related quality of life regarding micturition, sexual functioning and defecation.

However, when facing a complication thirty percent of women that decide to have a surgical correction, will need more than one surgical procedure and only 75% of women report symptom relieve after mesh revision surgery.

Until better treatment modalities will be available, we need to regulate the use of mesh. In the Netherlands the Dutch society of Gynaecology (NVOG) has created a consensus document regulating the use of mesh.[8] For patients with mesh-related complications a multidisciplinary mesh consortium has been instigated to optimize care for patients with mesh-related complications and the incentive to answer research questions regarding mesh implants. This will hopefully lead to better care for patients with mesh-related complications.

This thesis raised several new research questions. Future research should focus on the development of a prediction model as to which patients benefit most from surgical correction and a treatment algorithm should be developed to offer patients the best possible treatment. This algorithm should include surgical and non-surgical treatment options.

We need to further address the concern of patients regarding a systemic inflammatory response after PP implantation. This thesis did not show a causal relationship between this response and mesh implantation. However, these conclusions are based on retrospective data. We propose to perform a prospective cohort study measuring the immune status of patients prior to PP implantation.

In the meantime the search for other treatment options, such alternative scaffolds like for example absorbable mesh should be ongoing.

Part two: Peri-urethral bulking injections (PBI) with PDMS-U for stress-urinary incontinence.

Efficacy, risks and patient satisfaction of a relatively new bulking agent, PDMS-U.
In analogy to other implants, when injecting bulking material PDMS-U, this material is implanted into the body. At the time of performing the clinical studies for this thesis, PDMS-U was a relatively new bulking agent. We felt the need to thoroughly evaluate this bulking agent before implementation in standard care.

We set out to perform a prospective study in women that had a relative contra-indication for a mid-urethral sling for SUI. This study showed subjective improvement of 90% after 6 months follow up. The study population however was small, follow up was short and 40% of patients had a post-void residual volume of more than 150 mL.

To address satisfaction and safety of treatment with PDMS-U in the long term, we performed a cross-sectional study in 110 patients. This study showed that half of the patients were satisfied after 2 years of follow up. Various complications, such as urinary retention (22%), pain (15%), dyspareunia (15%), exposure (7%) and erosion (5%) were reported. The re-intervention rates were relatively high. In 6% of patients a reinjection of PDMS-U was indicated and in 18% bulking material had to be explanted. Fortunately, most complications were mild and transient, but because of the high complication and re-intervention rate and good alternative treatment options for SUI, most Dutch hospitals stopped offering this treatment.

Implication for daily practice and future perspective
Peri-urethral bulking
Although many hospitals in the Netherlands stopped offering bulking injection therapy with PDMS-U, we believe that bulking injection treatment in general is a good alternative option for mid-urethral sling (MUS) surgery.

The safety of mesh implants is under debate and medical authorities in many Anglo-Saxon countries have restricted the use of mesh implants. This stresses the need for alternative

treatment options for SUI. Bulking injection therapy is an ambulatory, minimal invasive treatment regimen for SUI and an alternative for MUS and other surgical procedures like a fascia sling or Burch colpo-suspension.

Although the efficacy is considered less than a MUS [28], patient preference studies show that women consider bulking injection therapy a valuable alternative treatment option compared to MUS performed under general or spinal anaesthesia.[29, 30]

The safety profile and efficacy of bulking injection therapy is dependent on the injected material.

The ideal bulking material should have a durable effect, be non-immunogenic, biocompatible, causing a minimal inflammatory and fibrotic response, and the particles should be large enough to stay in place.[31]

Over the years, many materials have been introduced but also withdrawn from the market due to reported (serious) complications. The ideal bulking material has yet to be found. Currently a relatively new bulking material, Polycaprolactone based bulking agent is under study in the Netherlands amongst other countries. This product should resorb completely over time and is supposed to induce neocollagenesis in urethral tissue with the effect of restoring urinary incontinence. Two-year follow up data of a pivotal trial has been published. The results of this study suggest that Polycaprolactone might be a safe and effective alternative for other bulking agents. However study groups were small and 22% was lost to follow up during the first 12 months.[32] Its safety and efficacy should be subject of further study.

Well-evaluated bulking material is Polyacrylamide Hydrogel. It has been used for many years and has been compared with the tension-free vaginal tape (TVT) in a non-inferiority clinical trial.[33] This data showed that women having a TVT were more satisfied and more frequent reported cure, but complication rates were lower for the Polacrylamide Hydrogel group and satisfaction and efficacy scores were also high.[28] Polyacrylamide Hydrogel is a bulking agent that is being offered in multiple centers in the Netherlands at this moment.

Altogether, women can benefit from the development of innovative products and techniques in pelvic reconstructive surgery. Efficacy and safety of new modalities should be well evaluated before implementation and there should be financial budget to develop and evaluate such innovative techniques. Physicians should keep this in mind when introducing and offering new treatment modalities to their patients.

References

1 Leidraad Nieuwe Interventies in de Klinische Praktijk 2014 [Available from: https://www.demedischspecialist.nl/sites/default/files/Leidraad%20Nieuwe%20interventies%20in%20de%20klinische%20praktijk%20def.pdf2021.

2 P. J. S. C. A. Campbell. *Vaginal mesh in prolapse surgery.* The Obstetrician and Gynaecologist 2018;20:49-56.

3 D. Karmakar & L. Hayward. *What can we learn from the vaginal mesh story?* Climacteric 2019;22(3):277-82.

4 Urogynecologic Surgical Mesh: Update on the safety and effectiveness of transvaginal placement for pelvic organ prolapse. : FDA, 2011.

5 M. Llamas. Transvaginal-mesh lawsuits, 2021:https://www.drugwatch.com/transvaginal-mesh/lawsuits/.

6 N. n. i. f. H. a. C. Excellence. Transvaginal mesh repair of anterior or posterior vaginal wall prolapse. Interventional procedures guidance [IPG599], 2017.

7 C. R. Chapple, F. Cruz, X. Deffieux, A. L. Milani, S. Arlandis, et al. *Consensus Statement of the European Urology Association and the European Urogynaecological Association on the Use of Implanted Materials for Treating Pelvic Organ Prolapse and Stress Urinary Incontinence*. Eur Urol 2017;72(3):424-31.

8 Leidraad Gebruik van Implantaten bij genitale prolaps - en urine-incontinentiechirurgie.

9 G. W. Cundiff, D. J. Quinlan, J. A. van Rensburg & M. Slack. *Foundation for an evidence-informed algorithm for treating pelvic floor mesh complications: a review.* BJOG 2018;125(8):1026-37.

10 A. L. Milani, A. Damoiseaux, J. IntHout, K. B. Kluivers & M. I. J. Withagen. *Long-term outcome of vaginal mesh or native tissue in recurrent prolapse: a randomized controlled trial*. Int Urogynecol J 2018;29(6):847-58.

11 J. N. Nguyen & R. J. Burchette. *Outcome after anterior vaginal prolapse repair: a randomized controlled trial*. Obstet Gynecol 2008;111(4):891-8.

12 N. Dykes, D. Karmakar & L. Hayward. *Lightweight transvaginal mesh is associated with lower mesh exposure rates than heavyweight mesh*. Int Urogynecol J 2020;31(9):1785-91.

13 M. I. Withagen, M. E. Vierhout, J. C. Hendriks, K. B. Kluivers & A. L. Milani. *Risk factors for exposure, pain, and dyspareunia after tension-free vaginal mesh procedure*. Obstet Gynecol 2011;118(3):629-36.

14 P. Collinet, F. Belot, P. Debodinance, E. Ha Duc, J. P. Lucot, et al. *Transvaginal mesh technique for pelvic organ prolapse repair: mesh exposure management and risk factors*. Int Urogynecol J Pelvic Floor Dysfunct 2006;17(4):315-20.

15 M. Donati, G. Brancato, G. Grosso, G. Li Volti, G. La Camera, et al. *Immunological reaction and oxidative stress after light or heavy polypropylene mesh implantation in inguinal hernioplasty: A CONSORT-prospective, randomized, clinical trial*. Medicine (Baltimore) 2016;95(24):e3791.

16 M. Endo, I. Urbankova, J. Vlacil, S. Sengupta, T. Deprest, et al. *Cross-linked xenogenic collagen implantation in the sheep model for vaginal surgery.* Gynecological Surgery 2015;12(2):113-22.

17 Y. H. Zhang, Y. X. Lu, X. Liu, W. J. Shen & J. X. Liu. *[Impact of vaginal mesh exposure on quality of life in patients undergoing transvaginal reconstructive pelvic surgery with polypropylene mesh].* Zhonghua Fu Chan Ke Za Zhi 2012;47(8):608-11.

18 A. L. Milani, M. I. Withagen, H. S. The, I. Nedelcu-van der Wijk & M. E. Vierhout. *Sexual function following trocar-guided mesh or vaginal native tissue repair in recurrent prolapse: a randomized controlled trial*. J Sex Med 2011;8(10):2944-53.

19 S. Warembourg, M. Labaki, R. de Tayrac, P. Costa & B. Fatton. *Reoperations for mesh-related complications after pelvic organ prolapse repair: 8-year experience at a tertiary referral center*. International Urogynecology Journal 2017;28(8):1139-51.

20 G. Agnew, P. L. Dwyer, A. Rosamilia, G. Edwards & J. K. Lee. *Functional outcomes for surgical revision of synthetic slings performed for voiding dysfunction: a retrospective study*. Eur J Obstet Gynecol Reprod Biol 2012;163(1):113-6.

21 N. F. Davis, L. G. Smyth, S. K. Giri & H. D. Flood. *Evaluation of endoscopic laser excision of polypropylene mesh/sutures following anti-incontinence procedures*. J Urol 2012;188(5):1828-32.

22 N. Abraham, I. Makovey, A. King, H. B. Goldman & S. Vasavada. *The effect of time to release of an obstructing synthetic mid-urethral sling on repeat surgery for stress urinary incontinence*. Neurourol Urodyn 2017;36(2):349-53.

23 G. F. Wolff, J. C. Winters & R. M. Krlin. *Mesh Excision: Is Total Mesh Excision Necessary?* Curr Urol Rep 2016;17(4):34.

24 J. W. Cohen Tervaert. *Autoinflammatory/autoimmunity syndrome induced by adjuvants (Shoenfeld's syndrome) in patients after a polypropylene mesh implantation*. Best Pract Res Clin Rheumatol 2018;32(4):511-20.

25 B. Chughtai, A. Sedrakyan, J. Mao, K. S. Eilber, J. T. Anger, et al. *Is vaginal mesh a stimulus of autoimmune disease?* Am J Obstet Gynecol 2017;216(5):495 e1-95 e7.

26 B. Chughtai, D. Thomas, J. Mao, K. Eilber, J. Anger, et al. *Hernia repair with polypropylene mesh is not associated with an increased risk of autoimmune disease in adult men*. Hernia 2017;21(4):637-42.

27 P. Muller, I. Gurol-Urganci, R. Thakar, M. R. Ehrenstein, J. Van Der Meulen, et al. *Impact of a mid-urethral synthetic mesh sling on long-term risk of systemic conditions in women with stress urinary incontinence: a national cohort study*. BJOG 2021

28 A. M. Itkonen Freitas, C. Isaksson, P. Rahkola-Soisalo, S. Tulokas, M. Mentula, et al. *Tension-Free Vaginal Tape and Polyacrylamide Hydrogel Injection for Primary Stress Urinary Incontinence: 3-Year Followup from a Randomized Clinical Trial*. J Urol 2022;208(3):658-67.

29 F. M. Casteleijn, R. A. Enklaar, I. El Bouyahyaoui, S. Jeffery, S. E. Zwolsman, et al. *How cure rates drive patients' preference for urethral bulking agent or mid-urethral sling surgery as therapy for stress urinary incontinence*. Neurourol Urodyn 2019;38(5):1384-91.

30 F. M. Casteleijn, S. E. Zwolsman, C. R. Kowalik & J. Roovers. *Patients' perspectives on urethral bulk injection therapy and mid-urethral sling surgery for stress urinary incontinence*. Int Urogynecol J 2018;29(9):1249-57.

31 V. Kirchin, T. Page, P. E. Keegan, K. O. Atiemo, J. D. Cody, et al. *Urethral injection therapy for urinary incontinence in women*. Cochrane Database Syst Rev 2017;7:CD003881.

32 E. L. O. Koldewijn, D.J.A.J.; Beulens, A.; de Wildt, M.J.A.M.; Vandoninck, V.; de Wachter, S;. *Treatment of mild to moderate stress urinary incontinence with a novel polycaprolactone-based bioresorbable urethral bulking agent*. Urogynaecologia 2022;2022(34)

33 A. M. Itkonen Freitas, T. S. Mikkola, P. Rahkola-Soisalo, S. Tulokas & M. Mentula. *Quality of life and sexual function after TVT surgery versus Bulkamid injection for primary stress urinary incontinence: 1 year results from a randomized clinical trial*. Int Urogynecol J 2021;32(3):595-601.

Chapter 9

Summary/ Samenvatting

Summary

This thesis evaluates the outcome of treatment with mesh implants for POP (part one) and the results of treatment with peri-urethral bulking agent PDMS-U for stress-urinary incontinence (SUI) (part two).

Chapter 1, the general introduction, gives an overview of the use of polypropylene (PP) mesh in pelvic reconstructive surgery and the use of peri-urethral bulking agents for SUI. This chapter describes the aims of the thesis.

Part one: Mesh implants

In **Chapter 2,** the results of a cross-sectional trial performed in 188 women who underwent vaginal mesh surgery are presented. The aim of the study was to explore long-term complications and patient satisfaction about treatment outcome of all women who underwent vaginal mesh surgery for POP in a Dutch University Hospital between 2007 and 2012.

Mesh surgery was performed in 188 women, in 147 (78%) because of recurrent POP. After a median follow-up of 40 months (range 12-76 months), 11 women (6%) had a symptomatic mesh exposure of whom 8 women underwent surgical re-intervention. Nine (5%) women had the novo pain following mesh surgery and in 3 women, (2%) this pain was persistent, despite additional treatment. Eighty-six percent of the responders reported to be satisfied about the outcome of their mesh surgery.

It was concluded that the prevalence of persistent pain and symptomatic mesh exposure symptoms was low in the investigated population. The overall satisfaction of vaginal mesh surgery was high.

Chapter 3 addresses the health-related quality of life (HR-QoL) in women after vaginal mesh surgery with and without mesh related complications. Mesh –related complications can have an impact on patients' live, but not all complications are symptomatic. Restoration of pelvic floor anatomy and improvement of pelvic floor function may compensate for the experienced discomfort of adverse events. The aim of this study was to investigate whether HR-QoL is comparable in women with and without a mesh complication.

To answer the research question, a cross-sectional trial was conducted. 128 women with a history of vaginal mesh surgery were included and were asked to fill out standardized QoL questionnaires; the Urogenital Distress Inventory-6 (UDI-6), the Incontinence Impact Questionnaire (IIQ), the Defecation Distress Inventory (DDI), and Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-12). Complications were registered according to the International Urogynecological Association (IUGA) complication classification.

Results show that in 29 (23%) patients a mesh-related complication occurred. The domain scores of the HR-QoL questionnaires showed no statistically significant differences between women with and without a mesh-related complication. A post hoc analysis showed similar HR-QoL for those in whom a mesh-related complication had been resolved and in those with persistent symptoms of the complication.

We concluded that patients should be counselled that the potential mesh-related complications do not negatively affect functional outcome related to micturition, defecation and sexual functioning.

Chapter 4 focuses on women with mesh-related complications and the potential benefit of surgical mesh revision to alleviate symptoms. The results of a cross-sectional trial that included 59 women who underwent mesh revision surgery between 2009 and 2016 is presented.

The primary outcome of interest was improvement after mesh revision surgery. Secondary outcome measures were Hr-Qol scores, surgical characteristics and physical findings at follow up visit.

All vaginal meshes were removed vaginally. In four cases abdominal mesh was approached by a vaginal, combined with an abdominal approach. This study showed that after a median follow-up of 1.7 (IQR: 1.1–2.4) years, 44 women (75%) reported reduction of symptoms. A trend in better Hr-Qol scores was seen in women that reported overall improvement after mesh revision surgery. One third of women were indicated for a subsequent operation following their mesh revision surgery.

This study facilitates in counselling women with mesh-related complications. Women should be informed that revision surgery alleviates symptoms in 75% of women, but in 29% more than one operation is indicated.

In **Chapter 5,** we systematically reviewed the literature to determine whether PP implants for inguinal, ventral hernia or pelvic floor surgery are associated with the development of systemic autoimmune syndromes. Speculation has arisen on consumer websites and discussion platforms that a multitude of systemic complaints can be attributed to polypropylene implants. Such an association would have huge impact on clinical practice, since only total mesh removal would hypothetically result in alleviation of systemic complaints. Such surgery is invasive and thus has a high risk on morbidity and would only be acceptable if the indication is indisputable.

After a systematic search, we identified four eligible studies. Two studies involving retrospective matched cohorts focusing on mesh surgery for vaginal prolapse and on inguinal hernia compared to respectively hysterectomy and colonoscopy. One

cohort study compared the incidence of systemic conditions in women having urinary incontinence surgery with and without mesh. These reports had a low risk of bias after quality assessment. A meta-analysis showed no association when comparing systemic disease between patients that had been implanted with polypropylene and control groups. Calculated Risk Ratio was 0.9 (95% CI 0.82-0.98). The fourth study was a case-series with a high risk of bias after quality assessment, with a sample of 714 patients with systemic disease, 40 of them had PP mesh implanted.

We concluded that there is no evidence to suggest a causal relationship between being implanted with a PP mesh and the occurrence of autoimmune disorders.

Part two:peri-urethral bulking

In **Chapter 6,** the results of a prospective study to assess efficacy and safety of peri-urethral bulking injections with an innovative bulking material (PDMS-U) are presented. PDMS-U was a relatively novel bulking agent at the time of the study and clinical evaluation of its effect and safety were indispensable before wide implementation.

We performed this study in women with SUI who, for several reasons, had a relative contraindication for a mid-urethral sling procedure. These reasons included: (i) recurrent SUI after a prior SUI surgical procedure; (ii) a history of oncologic gynaecological surgery; (iii) a history of neurologic disease resulting in voiding problems; (iv) a maximal flow rate of less than 15 mL per second or; (v) women with a contraindication for surgery with general or regional anesthesia.

This study showed that after 6 months follow up, 18 (90%) of the 20 included patients reported subjective improvement. Hr-QoI scores showed statistically significant improvement in all domain scores of the UDI-6, IIQ-7, and PISQ-12. Abnormal post voiding residual volume (>150 mL) was the most common adverse event, occurring in 40% of patients.

We concluded that PDMS-U is a viable treatment option in women with a relative contra-indication for mid-urethral sling surgery.

Chapter 7 focuses on patient satisfaction and safety of treatment with bulk injection therapy PDMS-U for SUI after long term follow up. 110 patients were included in this cross-sectional study. The primary outcome was patients' satisfaction, measured with the surgical satisfaction questionnaire (SSQ-8). The SSQ-8 answers were scored on a 5-point Likert scale ranging from "very satisfied" to "very unsatisfied" and from "yes" to "never". Patients were classified as satisfied when their answers corresponded with "very satisfied" and "satisfied" and "yes" or "maybe". Complications and re-interventions were deducted from medical charts and by face-to face interviews.

This study showed that after a median of 25 months (interquartile range: 14- 35 months) patients' satisfaction was 51%. Subjective and objective cure were respectively 46% and 47%. Various complications were seen of which urinary retention (22%), pain (15%), and dyspareunia (15%) were most prevalent. Exposure and erosion occurred in 7% and 5%, respectively. Re-intervention rate of reinjection and excision of bulk material was 6% and 18%, respectively. Objective cure significantly worsened during time-after-treatment (P = <.05).

We concluded that approximately half of patients is satisfied with peri-urethral bulking therapy with PDMS-U after 2 years of follow up. Clinical success and satisfaction were not influenced by body mass index or age. More patients with a previous surgical SUI procedure were objectively cured compared with conservative or no prior treatment (61% vs 37%; p =.04). A subgroup analysis on patient characteristics and the physician learning curve regarding complications did not show any variables that influenced the complication rate. Most complications were mild and transient, but approximately one fifth of patients required a re-intervention due to severe or persistent complications such as pain, exposure, or erosion.

Chapter 8 discusses the findings of this thesis and puts the results in broader perspective, including possible clinical implications.

Samenvatting

Dit proefschrift beschrijft de uitkomsten van behandeling met mesh implantaten vanwege vaginale prolaps (deel 1) en de resultaten van de behandeling met een peri-urethrale bulking agent (PDMS-U) vanwege stress-urine incontinentie (SUI) (deel 2).

Hoofdstuk 1 is de algemene introductie. Hierin wordt een overzicht gegeven van de achtergrond van operaties met polypropylene (PP) mesh implantaten vanwege vaginale prolaps en de behandeling van stress urine-incontinentie met peri-urethrale bulking. In dit hoofdstuk worden de onderzoeksvragen van dit proefschrift geformuleerd.

Deel één: *Mesh implantaten*

In **Hoofdstuk 2** worden de resultaten van een cross-sectionele studie weergegeven. 188 vrouwen die tussen 2007 en 2012 in een Nederlands Academisch Centrum een vaginale mesh operatie hebben gehad, werden geïncludeerd.

Het doel van de studie was om complicaties op de langere termijn en patiënt tevredenheid over de behandelingsuitkomsten van deze groep vrouwen in kaart te brengen.

De indicatie voor het verrichten van vaginale mesh chirurgie was bij 78% van de vrouwen een recidief prolaps. Na een mediane follow-up van 40 maanden (range 12-76 maanden), hadden 11 vrouwen (6%) een symptomatische mesh exposure, waarvoor 8 vrouwen een operatieve behandeling ondergingen. Negen (5%) vrouwen hadden de novo pijnklachten ontwikkeld, waarvan 3 vrouwen persisterende pijnklachten hadden, ondanks conservatieve of chirurgische therapie. 86% van de deelneemsters gaf aan tevreden te zijn met de mesh operatie.

Uit dit onderzoek hebben we de conclusie getrokken dat de prevalentie van pijn en symptomatische mesh exposure laag was in de onderzochte populatie. De algemene tevredenheid was hoog.

Hoofdstuk 3 beschrijft de kwaliteit van leven bij vrouwen die een operatie met een vaginaal mesh implantaat hebben gehad. Zowel de kwaliteit van leven bij vrouwen met en zonder een complicatie wordt beschreven.

Mesh gerelateerde complicaties kunnen een negatieve impact hebben op het dagelijks leven van vrouwen, maar niet alle complicaties zijn symptomatisch. Herstel van de pelviene anatomie en verbetering van de functionaliteit van de bekkenbodem kunnen tegenwicht bieden aan de nadelige effecten van een eventuele mesh gerelateerde complicatie.

Het doel van deze studie was om te onderzoeken of de gezondheid gerelateerde kwaliteit van leven vergelijkbaar is bij vrouwen met en zonder een mesh-gerelateerde complicatie.

Om deze onderzoeksvraag te beantwoorden, hebben we een cross-sectionele studie verricht. 128 vrouwen met een vaginale mesh operatie in de voorgeschiedenis werden geïncludeerd en gevraagd om de volgende gestandaardiseerde vragenlijsten te beantwoorden; Urogenital Distress Inventory-6 (UDI-6), the Incontinence Impact Questionnaire (IIQ), the Defecation Distress Inventory (DDI), and Pelvic Organ Prolapse/ Urinary Incontinence Sexual Function Questionnaire (PISQ-12).

Complicaties werden geregistreerd volgens de Internationale Urogynaecologische Associatie (IUGA) complicatieregistratie.

Er werd bij 29 (23%) vrouwen een mesh gerelateerde complicatie geconstateerd. De domein scores van de gestandaardiseerde kwaliteit van leven vragenlijsten lieten geen significante verschillen zien tussen vrouwen met en zonder een mesh gerelateerde complicatie. Een post hoc analyse liet vergelijkbare kwaliteit van leven uitkomsten zien voor vrouwen die een persisterende complicatie hadden, in vergelijking met vrouwen bij wie de complicatie was hersteld.

We hebben geconcludeerd dat patiënten voorgelicht moeten worden, dat een mesh gerelateerde complicatie geen negatief effect lijkt te hebben op de functionele uitkomsten zoals mictie, defecatie en seksuele functie.

In **Hoofdstuk 4** worden de uitkomsten van een studie gepresenteerd waarin we hebben gekeken of mesh revisie chirurgie bij vrouwen met een mesh-gerelateerde complicatie een positief effect heeft op de afname van klachten.

Om bovenstaande vraag te kunnen beantwoorden hebben we een cross-sectionele studie verricht, waarin 59 vrouwen geïncludeerd zijn die tussen 2009 en 2016 geopereerd zijn vanwege een mesh complicatie. De primaire uitkomstmaat was verbetering na revisie chirurgie. Secundaire uitkomstmaten waren kwaliteit van leven scores, chirurgische karakteristieken en uitkomsten van lichamelijk onderzoek ten tijde van het studiebezoek. Alle revisies van vaginale mesh implantaten zijn verricht via vaginale benadering. In vier patiënten met een abdominaal implantaat, was de chirurgische benadering vaginaal, gecombineerd met een abdominale benadering.

Dit onderzoek laat zien dat na een mediane follow-up van 1.7 (IQR: 1.1–2.4) jaar, 44 vrouwen (75%) een verbetering van klachten aangaven. Er werd een trend gezien waarbij vrouwen die een algemene verbetering na revisie chirurgie ervaarden ook beter scoorden op kwaliteit van leven. Eén derde van de vrouwen had meer dan 1 revisie operatie nodig. De uitkomsten van deze studie kunnen gebruikt worden bij de voorlichting van vrouwen die

een mesh revisie operatie overwegen. Vrouwen zouden geïnformeerd moeten worden dat zij 75% kans hebben op verbetering van hun klachten, maar bij 29% van de vrouwen is meer dan één operatie geïndiceerd.

In **Hoofdstuk 5** presenteren we systematisch literatuuronderzoek dat verricht werd om uit te zoeken of PP-implantaten die gebruikt worden voor inguinale, ventrale hernia of pelviene reconstructieve chirurgie, geassocieerd zijn met het ontstaan van systemische auto-immuun ziekten.

Er wordt op websites, discussieplatforms en lekenpers gespeculeerd dat een veelvoud aan systemische klachten te herleiden zouden zijn tot het gebruik van mesh implantaten. Als er een dergelijk verband zou bestaan, dan zou dit enorme consequenties hebben voor de behandeling van deze klachten. Dit zou betekenen dat alleen een volledige mesh resectie symptomen zou kunnen verlichten. Dit soort chirurgie heeft een hoog risico op morbiditeit en zou alleen acceptabel zijn als het verband onomstotelijk vast staat.

Nadat we een systematische zoekstrategie hebben uitgevoerd om relevante studies te vinden, hebben we een 4-tal studies kunnen includeren. Twee van deze studies waren retrospectieve studies met een gematchte controlegroep. Deze studies onderzochten PP mesh chirurgie voor de indicatie vaginale prolaps en inguinale hernia. Deze groepen werden gematcht met patiënten die een hysterectomie, dan wel een colonoscopie hadden ondergaan. Eén studie betrof een cohortstudie die de incidentie van systemische klachten onderzocht in vrouwen met stress-urine incontinentie, die met –en zonder implantaat werden behandeld. Een kwaliteitsanalyse liet een laag risico op bias zien.

Een meta-analyse liet geen associatie zien van systemische ziekte tussen de mesh en de controle groepen. De gecalculeerde risk ratio was 0.9 (95% CI 0.82-0.98). De vierde studie was een case-series met een sample van 714 patiënten met systemische ziekte, waarvan 40 patiënten een mesh-implantaat hadden. Een kwaliteitsanalyse liet een hoog risico op bias zien.

Uit dit literatuuronderzoek hebben we geconcludeerd dat er geen bewijs is dat er een oorzakelijk verband is tussen een geïmplanteerd mesh-implantaat en het ontstaan van auto-immuun ziekten.

Deel twee: peri-urethrale bulking

In **hoofdstuk 6** worden de resultaten van een prospectieve studie gepresenteerd. Deze studie is verricht om de effectiviteit en veiligheid van peri-urethrale bulking injecties met PDMS-U te onderzoeken. PDMS-U was een relatief nieuwe bulking agent ten tijde van de uitvoering van deze studie. Wij vonden het belangrijk om klinisch te evalueren wat de effectiviteit en veiligheid van het middel is.

We hebben voor deze prospectieve studie vrouwen geïncludeerd die een relatieve contra-indicatie hadden voor een mid-urethrale sling procedure. De relatieve contra-indicaties bestonden uit: (i) recidief SUI na een eerdere operatie voor SUI, (ii) een gynaecologisch-oncologische diagnose in de voorgeschiedenis, (iii) neurologische ziekte met mictie-problemen in de voorgeschiedenis, (iv) een maximale flow van 15 mL per seconde, (v) vrouwen met een contra-indicatie voor chirurgie met algehele of regionale anesthesie.

Deze studie liet zien, dat na een follow-up van 6 maanden, 18 (90%) van de 20 geïncludeerde patiënten een subjectieve verbetering van klachten ervaarde. Gezondheid gerelateerde domein scores lieten een significante verbetering zien in alle domein scores van de UDI-6, IIQ-7 en PISQ-12. De meest frequente complicatie was een residu na mictie van >150mL, dit kwam bij 40% van de patiënten voor.

Uit deze studie hebben we geconcludeerd, dat PDMS-U een behandeloptie is voor vrouwen met een relatieve contra-indicatie voor mid-urethrale sling chirurgie.

In **hoofdstuk 7** ligt de nadruk op patiënttevredenheid en veiligheid bij de behandeling van SUI met bulking injecties met PDMS-U op de langere termijn.

We hebben een cross-sectionele studie verricht, waarin 110 patiënten zijn geïncludeerd. De primaire uitkomstmaat was patiënttevredenheid. Deze werd gemeten met de “surgical satisfaction questionnaire” (SSQ-8). Deze vragenlijst scoort tevredenheid m.b.v. een 5 punt Likert schaal. Tevredenheid werd geclassificeerd als patiënten aangaven “zeer tevreden” of “tevreden” te zijn.

Complicaties en re-interventies werden geregistreerd uit status onderzoek en door middel van vragen ten tijde van het studiebezoek.

Deze studie laat zien dat na een mediane follow up van 25 maanden (interquartile range: 14- 35 maanden), de patiënt tevredenheid 51% was. Subjectieve en objectieve genezing waren 46% respectievelijk 47%. Er werden verschillende complicaties geconstateerd, waarvan urineretentie (22%), pijn (15%) en dyspareunie (15%) het meest prevalent waren. Exposure en erosie van bulking materiaal werd bij 7% respectievelijk 5% van de patiënten gezien.

Re-interventies zoals re-injecties en excisie van bulking materiaal werden bij 6%, respectievelijk 18% van de patiënten verricht. Objectieve genezing nam significant af in de tijd na behandeling (P = <.05). Uit deze studie hebben we geconcludeerd, dat ongeveer de helft van de behandelde patiënten met PDMS-U tevreden is na 2 jaar follow up.

Patiënt tevredenheid werd niet beïnvloed door leeftijd of body mass index. Patiënten die eerder een chirurgische behandeling voor incontinentie klachten hadden ondergaan,

gaven vaker aan objectief genezen te zijn, dan patiënten die geen eerdere behandeling of een conservatieve behandeling in de voorgeschiedenis hadden (61% vs. 37%; p =.04).

Een subgroep analyse van patiënt karakteristieken en de leercurve van de PDMS-U behandeling, liet geen variabelen zien de gerelateerd waren aan de aantallen complicaties.

De meeste complicaties waren van voorbijgaande aard en mild, maar ongeveer 1 op de 5 vrouwen behoefde een re-interventie vanwege ernstige en persisterende complicaties, zoals pijn, exposure en erosie van bulking materiaal.

In **hoofdstuk 8** worden de bevindingen van dit proefschrift bediscussieerd en worden de resultaten in breder perspectief geplaatst. Mogelijke klinische implicaties worden besproken.

Addendum

Funding of the studies
List of co-authors and their affiliations
List of co-authors and their contributions
PhD portfolio
Publications
Acknowledgements
Curriculum Vitae

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PhD Portfolio

Courses	Year	Workload (ECTS)
(Organisatie) Teach the teacher op maat	2022	0.5
IOTA- cursus	2021	0.5
Teach the teacher	2021	0.5
Postgraduate cursus kinder- en adolescentengynaecologie	2018	0.5
BROK	2017	1.5
11e WOG cursus gynaecologische oncologie	2015	1.0
Clinical Epidemiology	2013	0.9
Reference Manager bases	2010	0.2
Evidence Based Medicine	2009	0.5
Developing a Cochrane Systematic Review	2009	0.5
Verantwoord omgaan met medische statistiek	2007	0.2

Seminars, workshops and master classes	
Proctor Altis, Coloplast	2021-heden
Workshop Calister. Promedon. *Amsterdam*	2019
Opsys Workshop, Promedon. *Rome, Italy*	2019
Robotic assisted sacrocolpopexy workshop (Coloplast). *Hopital de Citadelle, Liège, Belgium*	2019
Proctor International stress urinary incontinence and surgical management course. *Skills centre Amsterdam*	2018
Proctor Second Coloplast European Masterclass for Pelvic Floor Surgery. *Amsterdam*	2018
Workshop Promedon. *Berlin, Germany*	2018
Workshop insertion BSC mesh. *Hagen, Germany*	2017
Proctor First Coloplast European Masterclass for Pelvic Floor Surgery. *Amsterdam*	2017
Workshop Female Pelvic Health (Restorelle/ Altis insertion). *Paris, France*	2016
Urgent PC-symposium	2014
Opname SAVE'R instructie dvd schouderdystocie en stuitbevalling	2009

(Inter)national conferences attended	Year	Workload (ECTS)
EUGA conference (Antibes, France)	2022	0.5
Gynaecongres	2022	0.5
45th IUGA conference (Virtual)	2020	0.5
34th ICS conference (Virtual)	2020	0.5
12th EUGA conference (Tel Aviv, Israel)	2019	0.5
22e IGO- Doelencongres (Rotterdam)	2019	0.5
43rd IUGA conference (Vienna, Austria	2018	0.5
54e Gynaecongres	2018	0.5
42nd IUGA conference (Vancouver, Canada)	2017	0.5
52e Gynaecongres	2017	0.5
21e IGO--Doelencongres (Rotterdam)	2017	0.5
49e Gynaecongres	2016	0.5
COBRAdagen (Noordwijkerhout)	2016	0.5
9th EUGA conference (Amsterdam, the Netherlands)	2016	0.5
ICS conference (Tokyo, Japan)	2016	0.5
47e Gynaecongres	2015	0.5
40th IUGA conference (Nice, France)	2015	0.5
20e IGO-doelencongres (Rotterdam)	2015	0.5
39th IUGA conference (Washington DC, United States)	2014	0.5
EUGA conference (Athens, Greece)	2014	0.5
45e Gynaecongres (Leeuwarden)	2014	0.5
COBRA dagen (Noordwijkerhout)	2014	0.5
38th IUGA conference (Dublin, Ireland)	2013	0.5
EUGA conference (Berlin, Germany)	2013	0.5
19e IGO- Doelencongres (Rotterdam)	2013	0.5

Presentations

Complicaties van bekkenbodem chirurgie
Complicatiedagen, Amsterdam 2022

Pelvic Organ Prolapse.
Post ICS en IUGA-congres 2021, (Virtual)

Vaginale mesh.
Werkgroep bekkenbodem NVOG, Houten 2019

Mesh related complications do not negatively affect quality of life.
43rd IUGA scientific meeting, poster and oral presentation, Vienna, Austria. 2018

Clinical effectiveness of a new generation peri-urethral bulking injection in women with stress urinary incontinence and a poor prognostic profile.
ICS meeting, poster and oral presentation, Tokyo, Japan 2016

A mesh recall in response to the FDA-Report; a single centre report.
39th AUGS/ IUGA scientific meeting, poster and oral presentation, Washington, United States. 2014

Behandeling stress-incontinentie: minder opereren meer injecteren?
Cobradagen 2016

Wat is de toegevoegde waarde van bulking agents?
IGO- Doelencongres, 2015

De ratio van behandeling van de uterus septus bij vrouwen met herhaalde miskraam en subfertiliteit. *Symposium Jonge Zwangerschap*

Anatomic factors and recurrent pregnancy loss**.**
ESHRE Campus, Manchester, United Kingdom 2009

Uterusanomalieën; is hysteroscopische behandeling zinvol?
IGO- Doelencongres 2009

Pre-eclampsie.
Wetenschapssymposium, Spaarne Ziekenhuis 2008

Other

2008-2013

Uitvoerend onderzoeker van de “randomized uterine transection trial” (TRUST). Een RCT naar hysteroscopische septumresectie versus expectatief beleid, bij vrouwen met herhaalde miskraam en subfertiliteit.

Lecturing

Toegepaste anatomie, gevorderden cursus.
Amsterdam 2021

Zorg voor de bekkenbodem; nascholing medisch specialisten.
Amsterdam 2018

Interdisciplinair Incontinentie en Prolaps Overleg**;** nascholing medisch specialisten.
Amsterdam, 2017

Themadag Gynaecologie: De bekkenbodem in beeld**.**
Amstelacademie, Amsterdam 2017

Interdisciplinair Incontinentie en Prolaps Overleg**;** nascholing medisch specialisten.
Amsterdam, 2016

Tot op de bekkenbodem; huisartsennascholing.
Amsterdam 2016

Onderwijs betreffende de bekkenbodem aan verpleegkundigen.
Amstelacademie, Amsterdam 2016

Tot op de bekkenbodem, huisartsennascholing.
Amsterdam 2015

Tutoring, Mentoring

Onderwijs studenten opleiding geneeskunde en co-assistenten (2013- heden)

Stagebegeleider arts-assistenten Urogynaecologie (2018- heden)

Klinische lessen verpleegkundigen (2013- heden)

Mentoring: M. van Zummeren (2022- heden)

Supervising	Year	Workload (ECTS)
Krista van Rest, PhD	2021- heden	1.0
Rosanne Grolle, (ANIOS)	2020	0.5
Benjamin Tros, bachelor thesis	2015	1.0

List of publications

PubMed Publications

Kowalik CR, Mol BW, Veersema S, Goddijn M. Critical appraisal regarding the effect on reproductive outcome of hysteroscopic metroplasty in patients with recurrent miscarriage. *Arch Gynecol Obstet. 2010 Oct;282(4):465.*

Kowalik CR, Goddijn M, Emanuel MH, Bongers MY, Spinder T, de Kruif JH, Mol BW, Heineman MJ. Metroplasty versus expectant management for women with recurrent miscarriage and a septate uterus. *Cochrane Database Syst Rev. 2011 Jun 15; (6):CD008576*

De Kraker AT, **Kowalik CR**, Roovers JPWR. Operatieve behandeling van complicaties van vaginale prolapschirurgie met implantaat ("mesh"). *Ned Tijdschr Geneeskd. 2015;160: A9693*

Kowalik CR, Lakeman ME, Oryszczyn JE, Roovers JPWR. Reviewing patients following mesh repair; the benefits. *Gynecol Obstet Invest. 2016 Dec 29*

Rikken JF, **Kowalik CR**, Emanuel MH, Mol BW, Van der Veen F, van Wely M, Goddijn M. Septum resection for women of reproductive age with a septate uterus. *Cochrane Database Syst Rev. 2017 Jan 17;1:CD008576*

Kowalik CR, Casteleijn FM, van Eijndhoven HWF, Zwolsman SE, Roovers JPR
Results of an innovative bulking agent in patients with stress urinary incontinence who are not optimal candidates for mid-urethral sling surgery. *Neurourol Urodyn. 2018 Jan;37(1):339-345*

Casteleijn FM, Zwolsman SE, **Kowalik CR**, Roovers JPWR. Patients' perspectives on urethral bulk injection therapy and mid-urethral sling surgery for stress urinary incontinence. *Int Urogynecol J. 2018 Apr 19*

Kowalik CR, Lakeman MME, de Kraker AT, Roovers JPWR. Effects of mesh-related complications in vaginal surgery on quality of life. *Int Urogynecol J. 2018 Jun 16*

Rikken JFW, **Kowalik CR**, Emanuel MH, Bongers MY, Spinder T, de Kruif JH, Bloemenkamp KWM, Jansen FW, Veersema S, Mulders AGMGJ, Thurkow AL, Hald K, Mohazzab A, Khalaf Y, Clark TJ, Farrugia M, van Vliet HA, Stephenson MS, van der Veen F, van Wely M, Mol BWJ, Goddijn M. The randomised uterine septum transsection trial (TRUST): design and protocol. *BMC Womens Health 2018 Oct 5;18(1):163*

Casteleijn FM, **Kowalik CR**, Berends C, Blaganje M, Pecev ML, van der Linden E, Zwolsman SE, Roovers JPWR, Minnee P. Patients' satisfaction and safety of bulk injection therapy

Urolastic for treatment of stress urinary incontinence: A cross-sectional study. *Neurourol Urodyn 2020 Aug;39(6):1753-1763*

Kowalik CR, Lakeman MME, Zwolsman SE, Roovers JWR. Efficacy of surgical revision of mesh complications in prolapse and urinary incontinence surgery. *Int Urogynecol J. 2020*

Rikken JWF, **Kowalik CR**, Emanuel MH, Bongers MY, Spinder T, Jansen FW, Mulders AGMGJ, Padmehr R, Clark TJ, van Vliet HA, Stephenson MD, van der Veen F, Mol BWJ, van Wely M, Goddijn M. Septum resection versus expectant management in women with a septate uterus: an international multicentre open-label randomized controlled trial. *Hum Reprod. 2021 May; 36(5): 1260–1267*

Kowalik CR, Zwolsman SE, Malekzadeh A, Roumen RMH, Zwaans WAR, Roovers JPWR. Are polypropylene mesh implants associated with systemic autoimmune inflammatory syndromes? *A systematic review. Hernia. 2022 Apr;26(2):401-410*

Kowalik CR, Zwolsman SE, Malekzadeh A, Roumen RMH, Zwaans WAR, Roovers JPWR. Are polypropylene mesh implants associated with systemic autoimmune inflammatory syndromes? Author's reply*, et al. Hernia. 2022 Aug;26(4):1205*

Vodegel E, van Delft KWM, Nuboer CHC, **Kowalik CR,** Roovers JPWR. Surgical management of pudendal nerve entrapment after sacrospinous ligament fixation. *BJOG 2022 Oct;129(11):1908-1915*

Vodegel E, van Delft KWM, Nuboer CHC, **Kowalik CR,** Roovers JPWR. Authors' reply: Surgical management of pudendal nerve entrapment after sacrospinous ligament fixation. *BJOG 2022 Oct;129(11):1943*

Casteleijn FM, de Vries AM, Heesakkers JPFA, Latul Y, **Kowalik CR**, van Eijndhoven HWF, van Eekelen R, Roovers JPWR. Cost-effectiveness of urethral bulking polydimethylsiloxane-Urolastic compared to mid-urethral sling surgery for stress urinary incontinence: a two-arm cohort study. *BJOG. 2023 Jan 20. Online ahead of print*

Casteleijn FM, Zwolsman SE, Latul Y**, Kowalik CR**, Roovers JPWR. Learning curve of urethral bulk injection therapy polydimethylsiloxane –Urolastic for female stress urinary incontinence. *Submitted*

van Rest KLC, Gielen MJCAM, Warmerdam LM, **Kowalik CR**, Roovers JPWR, Zwaans WAR. Prediction of successful revision surgery for mesh-related complaints after inguinal hernia and pelvic organ prolapse repair. *Accepted for publication in Hernia.*

Other publications

Koot YEM, **Kowalik CR**, Goddijn M. Reactie op artikel: Voortgaande discussie over herhaalde miskraam. *NTOG 2011 April; 124(03): 121*

De Jong PG, van den Boogaard E, **Kowalik CR**, Vissenberg R, Middeldorp S, Goddijn M. Recurrent Pregnancy Loss. Chapter 2. Which investigations are relevant? Edited by Ole B. Christiansen. First published 2014© by John Wiley &Sons, Ltd

Kowalik CR, Zwolsman SE, Jonker MP, Roovers JP, Is er een verband tussen polypropyleen implantaten voor prolaps en het ontstaan van auto-immuunziekten? *NTOG maart 2020*

Overbeek A, Gerbrandy-Schreuders LC, Roovers JP, **Kowalik CR,** Abdominale transvesicale benadering voor mesh-erosie in de blaas. *NTOG 2021*

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Curriculum Vitae

Claudia Kowalik werd geboren op 25 juni 1979 in Hilversum. Na het behalen van haar VWO diploma aan het Gemeentelijk Gymnasium te Hilversum, werd zij uitgeloot voor de studie Geneeskunde, waarop zij in 1997 startte met de studie Nederlands Recht aan de Universiteit van Amsterdam. Zij rondde het eerste jaar rechten af met een Propedeuse Nederlands Recht. In 1998 werd zij alsnog ingeloot voor de studie Geneeskunde aan de Universiteit van Amsterdam en behaalde zij in 2004 haar artsexamen.

Haar eerste banen als arts waren als arts-assistent Heelkunde in het Vlietland Ziekenhuis in Schiedam en vervolgens als arts-assistent Obstetrie en Gynaecologie in het Zaans Medisch Centrum te Zaandam. In 2006 begon zij met de specialisatie tot gynaecoloog, welke zij volgde in het Spaarne Gasthuis en het Amsterdam UMC, locatie AMC.

Tijdens haar specialisatie raakte zij geboeid door de bekkenbodem problematiek en sloot zij haar specialisatie tot gynaecoloog af met een differentiatie bij de Urogynaecologie in het Amsterdam UMC en Bergman Clinics Vrouw.

Sinds 2013 werkt Claudia als gynaecoloog bij het Amsterdam UMC en Bergman Clinics Vrouw, eerst in de rol van fellow Urogynaecologie en sinds 2014 als staflid met aandachtsgebied Urogynaecologie.

Claudia woont samen met Steven Zeeman in Nootdorp met haar en Steven zijn kinderen; Belle, Quirijn, Oscar, Victor en Anna.

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