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*A multiperspective evaluation*

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# Urethral bulk injection therapy for female stress urinary incontinence: a multiperspective evaluation

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# General introduction and outline of the thesis

## GENERAL INTRODUCTION

Female stress urinary incontinence is defined as the leakage of urine when women laugh, sneeze, cough or exercise, and is perceived as a distressing, embarrassing and humiliating experience (1, 2). As a result, woman's social and sexual relationships are negatively affected and quality of life (QoL) is often significantly reduced (2-4). SUI is the most common type of urinary incontinence and has an estimated pooled prevalence rate of 30% (5). Prevalence rates increase with age, but pregnancy, vaginal childbirth and parity are major risk factors for SUI (6). Given its high prevalence and QoL-impairing nature, SUI is a global health care burden that generates high costs.



The etiology of SUI is not fully understood, but believed to be a combination of the two following factors, in which one or the other is more in the foreground. The first factor is failure of the urethra support system, due to damage of the surrounding fasciae and muscles (7). Damage of the surrounding tissue is most often caused by childbirth or surgery. A failing support system seems to inhibit the 'hammock-like structure' which is necessary for the urethra to close during increased abdominal pressure (for example while laughing, sneezing or coughing) (8). Intrinsic sphincter deficiency (ISD) is considered the second factor in the etiology of SUI. ISD is the suboptimal function of the muscle in the urethra (urethral sphincter) which can be caused by age-related reduction of sphincter muscle mass or damage to the nerve that innervates the sphincter (pudendal nerve damage) (9, 10). So SUI is a combination of both factors, with ISD being more prominent in the more severe cases.

Health-seeking behavior among patients with SUI is poor since only about half consult their physician and delay their visits with many years after initiating of symptoms (11). The reasons that patients do not seek help vary. Some patients believe their symptoms are 'mild' or can be adequately managed by themselves, while others feel embarrassed to seek help or believe SUI is part of aging (12).

The range of treatment options for SUI cover all degrees of invasiveness, from disposable, absorbable pads to invasive interventions. Guideline recommendations are to start with non-invasive treatments before moving on to interventions. A common and effective first step in treating (mild) SUI is pelvic floor muscle training (PFMT). PFMT is an effective treatment compared to non-treatment, although it requires high patient motivation to maintain practice for at least three months (13). The best option for a cure is surgical treatment, which is mostly favoured for patients with bothersome symptoms after first-line therapy. Several surgeries are recommended by international guidelines: mid-urethral sling (MUS) surgery, autologous fascial sling, colposuspension and bulk injection therapy (14). The European Association of Urology (EAU) states that the surgical options vary in invasiveness, efficacy and safety and shared-decision making approach is paramount for treatment selection. The choice of surgical treatment is a

balanced trade-off between the preference of both patient and physician, the patient's characteristics and the physician's experience. Patient decision aids, involving benefits and risks of the optional surgeries, have been put forward to promote shared-decision making (15). The approach of MUS-surgery, autologous fascial sling and colposuspension is to mimic the hammock design by lifting and supporting the urethrovesical junction or urethra. MUS-surgery is one of the most used surgical option, because of its high chance of success and acceptable safety profile. With MUS-surgery a synthetic mesh is inserted at mid-urethral level through transobturator route (TOR) or retropubic route (RPR). Reported long term subjective success rates for TOR and RPR are 43-92% and 51-88% respectively (16). A separate group among mid-urethral slings are single-incision mid-urethral sling (SIMS) operations. SIMS was invented to avoid MUS-related serious-adverse-events (SAE), such as persistent groin pain (from TOR) and bladder perforations (from RPR). As yet, not enough evidence has been published on SIMS to compare success rates with TOR and RPR (17).

## BULK INJECTION THERAPY

Bulk injection therapy, the focus of this thesis, has a different mechanism of action; it focuses on improvement of the urethral sphincter function and enhance compression and coaptation of the mucosa by injecting mechanical barriers ('bulk') beneath urethral mucosa. The bulk material is injected either trans-urethrally under cystoscopic view or peri-urethrally without cystoscopic view. With trans-urethral injection the cystoscopic view determines the exact location of the injection and the amount of the bulk material is adjusted to the degree of coaptation. This may have an advantage with regard to the consistency of the injection. However, a randomized trial showed both routes to be equally efficacious although the peri-urethral route was associated with higher rates of post-operative urinary retention (18). Benefits of bulk injection therapy is that the procedure has a minimally invasive character since it is carried out under local analgesia and can be performed in a non-surgical environment. Moreover, bulk injection therapy has a beneficial safety profile with lower adverse event rates compared to open surgery (level of evidence 2A) (19). However, bulk injection therapy is less effective than mid-urethral sling (MUS) surgery, autologous fascial sling and colposuspension (level of evidence 1B)) . International guidelines do not state which patient population would benefit most from bulk injection therapy and currently it can be offered as primary surgical procedure, secondary treatment option after failed surgery or as last resort after multiple failed surgical treatments. The EAU states that a thorough discussion of the risks and benefits of bulk injection therapy relative to other surgeries should be held before offering it to patients. EAU recommends that patients should be informed

that long-term durability for this treatment is not established and repeat injections could be necessary (20).

*History of bulking agents*

Urethral bulking agents were first used for bulk injection therapy in women with SUI in 1938 and since many different bulking agents have been introduced (21). Significant safety issues prevented some UBA from being widely implemented. Particle migration and embolisms to the brain, lung and lymph-nodes were described for polytetrafluoroethylene (Teflon™), and autologous fat, high numbers of urethral erosions and pseudo-abscess formation were reported for ethylene vinyl alcohol copolymer (EVOH) (Uryx™) and hyaluronic acid with dextranomer (Zuidex™) respectively. As a result, these bulking agents were retracted from the market. It became clear that particles should be at least 80 μm in size to prevent migration and that the material must be biocompatible, i.e. the material should not trigger inflammatory or immunological responses. Furthermore, the ideal bulking agent should be easily injectable, consistently located, effective, safe and durable. Glutaraldehyde cross-linked bovine collagen (Contigen®) was the first widely used and well-studied bulking agent that was approved by the Food and Drug Administration (FDA), but stopped continuing production due to delayed skin reactions and arthralgia.

Currently, several bulking agents are approved for the use for SUI by the US Food and Drug Administration (FDA) or have a CE-mark: poly-dimethyl-siloxane macro particles (Macroplastique™), polyacrylamide hydrogel injection (PAHG) (Bulkamid®), calcium hydroxylapatite (CaHA) (Coaptite™), porcine dermal (Permacol™), carbon-coated zirconium beads (Durasphere®) and polydimethylsiloxane-Urolastic (PDMS-U) (Urolastic®). Each of these bulking agents have their own characteristics. Generally speaking, bulking agents can be divided in two groups: bulking agents that consists of solid microparticles in an absorbable gel carrier (Macroplastique™, Coaptite™, Durasphere®) and bulking agents that consist of a non-particular (partly) non-absorbable, migration resistant homogenous gel (Bulkamid®, Urolastic®) (22). The second group may be hypothetically more durable because of its non-degradable character, however there is minimal data comparing the two groups (22). The difference between Bulkamid® and Urolastic® is that Bulkamid® is a polyacrylamide hydrogel that mainly consists of water (97.5%), while Urolastic® is an inert silicon-based polymer that polymerize into a uniform elastomer (a 'rubber' with properties of viscosity and elasticity). Complications that are described (such as hematuria, pain, post-procedural urinary retention, urinary tract infections and urinary urgency or frequency symptoms) are mostly mild, transient without an indication for re-intervention (23).

**Evidence of bulk injection therapy**

The bulking agents available are studied moderately. The last Cochrane update in 2012 concluded that the available evidence remains insufficient to guide practice (24). More recently, a systematic review showed that there is a long list of cohort studies, but with only a few RCTs. This review reported an overall short-term (<24 months) efficacy rate of 30-80% (of bulking agents: Bulkamid®, Macroplastique™, Durasphere®, Coaptite® and Urolastic®). Bulkamid® and Macroplastique® were studied the most, and had short-term efficacy rates of 30%-90% and 40%-85% respectively. Bulkamid® had a better safety profile, because erosion and particle migration did not occur (25). There are no studies of the current available bulking agents that compared bulk injection therapy to 'no treatment'. One study randomized bulk injection therapy with PFMT: poly-dimethyl-siloxane macro particles (Macroplastique™) (n=24) versus PFMT (n=21), showing better success rates at three months follow-up for Macroplastique™ as well as more adverse events (26). No randomized trials are available of the current available bulking agents comparing each other. Durasphere®, Macroplastique™, PAHG Bulkamid® and CaHa Coaptite™ have been compared in randomized trials to Glutaraldehyde cross-linked bovine collagen (Contigen®), however this bulking agent is not available anymore. Durasphere®, PAHG Bulkamid® and CaHa Coaptite™ showed no difference in success rates to Contigen®, whereas Macroplastique™ showed higher cure rates (27-29). Two randomized trials have been published of current available bulking agents compared to other surgical modalities. Maher et al compared pubovaginal sling (n = 22) with transurethral Macroplastique™ (n = 23) showing similar subjective symptom improvement and satisfaction rates at 12 months follow-up, but higher objective cure rates were found for pubovaginal sling (30). Itkonen Freitas et al reported that mid-urethral tension-free vaginal tape slings showed better satisfaction and cure rates than polyacrylamide hydrogel injection (PAHG) (Bulkamid®) (31).

**Bulking agent polydimethylsiloxane-Urolastic®**

The latest bulking agent introduced is polydimethylsiloxane-Urolastic (PDMS-U) (Urolastic®, Urogyn BV) which will be discussed in this thesis. PDMS-U consists of a biocompatible, large polydimethylsiloxane polymer, but is merged with a second substance during injection: tetrapropoxysilane cross-linking agent that is a platinum divinyltetramethyl siloxane complex catalyst and titanium dioxide radio-pacifying agent. This mixture causes the substance to polymerise, resulting in a smooth, solid mass. The same material has been used from 1988 for hysteroscopic tubal plugging (Ovabloc) for women looking for sterilization, but was withdrawn from the market around 2009 because of discouraging results, technical storage problems and a claim about the reversibility of the technique (32, 33). PDMS-U is not absorbed by the body which, hypothetically, could imply a long-lasting result. The procedure takes around 20 min-

utes with Lidocaine analgesia. Using a disposable injection-device, bulk deposits are injected peri-urethrally around the urethra at mid-urethral level. The optimal location and size of the bulk deposits has not been researched. The current training manual from Urogyn BV reports to use 0.8-1.0 cc at 2, 5, 7, and 10 o'clock. The recovery period is short, but lifestyle restrictions include no heavy lifting, no sexual intercourse and no bathing for 2-6 weeks. In 2012 when PDMS-U received its CE-mark, Urolastic® was branded as a new, minimally invasive option to treat uncomplicated SUI.
Two prospective cohort studies were performed and showed promising results for patients that underwent PDMS-U as the primary intervention; with QoL significantly improving and 68% of patients objectively reporting dry after a 12 month follow-up (34). Patients receiving PDMS-U for recurrent or persistent SUI after surgery also showed acceptable objective cure rates of 59%. Moreover, no serious adverse events were reported. Based on these studies it was concluded that PDMS-U was a safe and effective alternative treatment option and PDSM-U was subsequently adopted by different health care providers throughout the Netherlands and abroad.



Despite this, several knowledge gaps remain and a research line in collaboration with Amsterdam UMC was established in 2014 to address this. The aim of this research line was first to evaluate the patients' perspective to determine if and why PDMS-U would be a valuable alternative to existing treatment options. A second aim was to improve knowledge on the indication for PDMS-U by gaining more evidence on efficacy, safety, re-intervention rates, sexual function and the physicians learning curve. Thirdly, the value of PDMS-U from an economic perspective could be investigated by performing a cost-effectiveness analysis. The results of these research questions, conveyed in this thesis, will provide better information for physicians for shared-decision making.

## OUTLINE OF THE THESIS

**Chapter 2** is a qualitative study focusing on factors that influenced patients' decision-making between PDMS-U and MUS-surgery in order to understand why patients would prefer PDMS-U or not. **Chapter 3** is a treatment trade-off patients' preference study that investigated how effective PDMS-U should be compared to MUS-surgery to prefer this treatment. These two patients preference studies will provide insight when and why patients would opt for PDMS-U compared to MUS-surgery. **Chapter 4** is a cross-sectional study in patients being treated with PDMS-U after a median of two years ago to determine the patients' satisfaction, safety and re-intervention rate of PDMS-U. **Chapter 5** reports the benefits and risks six months after being treated with PDMS-U in patients who are poor candidates for surgery. **Chapter 6** is a cost-effectiveness analysis to determine the if money is best spend on MUS-surgery or

PDMS-U in patients with moderate to severe SUI. **Chapter 7** investigates the impact of PDMS-U on the sexual function. **Chapter 8** shows the physicians' learning curve of PDMS-U and the impact of physicians' expertise on safety outcomes, in order to learn how to organize health care for PDMS-U. **Chapter 9** gives a summary of all chapters. **Chapter 10** discusses the results of the thesis and implications for clinical practice and future research.

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# Chapter 2

# Patients' perspectives on urethral bulk injection therapy and mid-urethral sling surgery for stress urinary incontinence

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## ABSTRACT

### Introduction and hypothesis

The aim of this study was to identify all treatment decision factors that determined the preference for peri-urethral bulk injection therapy (PBI) or mid-urethral sling (MUS) surgery in patients with primary stress urinary incontinence (SUI). Second, we explored what patients expect from treatment for SUI and whether patients would consider PBI as a primary treatment option.

### Methods

In a qualitative design, 20 semi-structured, face-to-face interviews were conducted in women with primary SUI. Exclusion criteria were: previous PBI or MUS surgery; predominating urgency. Interviews were guided by three open-ended questions and a topic list. PBI treatment and MUS surgery were described in detail, and the efficacy was stated as 70% and 90%, respectively. Data saturation was reached when no new treatment decision factors were identified in three consecutive interviews. Interviews were audiotaped and fully transcribed. Thematic analysis by a coding process was done independently by two researchers.

### Results

Sixteen procedural, personal, professional, social and external treatment decision factors were identified. Regarding expectations about treatment for SUI, women believed 'becoming dry' was wishful thinking. The majority of patients accepted a small degree of persistent urinary incontinence after treatment. Regardless of their treatment preference, patients indicated that women should be informed about PBI as a primary treatment option.

### Conclusion

Patients with primary SUI are open to PBI as an alternative treatment option even with lower cure rates compared with MUS surgery performed under general or spinal anesthesia. Patients indicated that women with primary SUI seeking treatment should be informed about PBI as a treatment option.


**Keywords:** Stress urinary incontinence, Urethral injection therapy, Mid-urethral sling surgery, Treatment preference

## INTRODUCTION

Stress urinary incontinence (SUI), defined as the involuntary leakage of urine on exertion or sneezing or coughing, is a major public health issue affecting up to 45% of women (1–3). Several treatment options for SUI are available, and treatment decisions are based on international guidelines and both the physician and patient preference. Pelvic floor muscle training (PFMT) is considered a valuable first option, since PFMT has a negligible risk of complications and achieves a patient-reported cure rate of 56% (4). Mid-urethral sling surgery is considered the first surgical option because of the high efficacy rates (5–7). Besides PFMT and MUS surgery, various alternative treatment options are available, including peri-urethral injection therapy (PBI). However, even though patients with SUI want to be informed about their treatment options and to be involved in treatment decision-making (8, 9), they are often unaware of PBI as a treatment option.



The hypothesis of the efficacy of PBI is that it compresses the urethra and improves urethral coaptation by injecting a synthetic biomaterial peri-urethrally. One benefit of PBI is that the procedure can be performed under local analgesia in an office setting. Second, the Cochrane Review reports that bulk injection therapy has a better safety profile compared with open surgery (10). Although a prospective cohort study of PBI after 1-year follow-up showed promising results with cure rates of 70% (11), randomized trials comparing PBI and MUS surgery and long-term follow-up data are lacking. Therefore, PBI is not recommended as a first-line therapy and is mainly offered to patients who have a contraindication for MUS surgery or to patients with complex or recurrent SUI (10, 12–14). Petrou et al. showed, however, that injection therapy could still be the first choice treatment for patients who attach more value to a less invasive procedure (15). This suggests that the cure rate is not always decisive in selecting the right treatment for the right patient.

To explore whether patients consider PBI a reasonable primary treatment option for SUI, one should first understand the patients' perspectives or the expectations that underlie their motivation for PBI instead of standard treatment. This insight increases the understanding of patient decision-making and helps physicians to address the correct items in shared decision-making.

In this qualitative study, we primarily aimed to identify all treatment decision factors that determine the preference for PBI and MUS surgery in patients with primary SUI. Second, we aimed to explore what patients expect from treatment for SUI in general and whether patients would consider PBI as a primary treatment option for SUI.

## METHODS

This qualitative study focused on patient perspectives on factors to take into account when choosing between PBI and MUS surgery. The methods and results of this study are reported according to the consolidated criteria for reporting qualitative research (COREQ) (16).

### Recruitment

Patients with SUI were recruited at a tertiary urogynecologic center in The Netherlands where about 700 women with urinary incontinence are seen per year. To be eligible, women had to be Dutch-speaking and seeking treatment for SUI. Patients with predominant urgency incontinence or a history of MUS surgery or PBI treatment were not eligible. It was hypothesized that patients of different ages and different perceived severities of symptoms would have different perspectives concerning SUI treatment. Therefore, the investigator selected the participants until wide ranges of ages and of patients with mild, moderate and severe SUIs were adequately represented. This method of recruitment is called purposive sampling (17). Eligible patients were informed about the study by an information leaflet, and those not willing to participate were asked to give a reason. The sample size was completed when data saturation occurred, meaning that more interviews would not lead to more information (18, 19). Data saturation was reached when no new treatment decision factors were observed in three consecutive interviews (20). The ethics board confirmed that the Dutch 'Medical Research Involved Human Subjects Act' did not apply to this study and that no further review was required.

### Topic list and interview

The interviews had a face-to-face format, and the interviewer relied on a semistructured interview guide with three open-ended questions and a framework of topics to discuss. This open format allowed following the narrative of patients and picking up on all factors they brought up rather than following fixed or loose sequences of predefined questions, as in structured or semi-structured interviews, respectively (21). Predetermined topics were: anesthesia, efficacy, complications, safety, setting, recovery and postoperative pain, re-interventions and sexual function. The contents of the topic list were compiled by an expert panel of two urogynecologists [CK; JR] and an experienced researcher in the field of qualitative research [SZ]. The interviews were conducted by a female researcher with a medical doctor's degree [FC] who pilot tested the topic list on two women with SUIs. After pilot testing, no new topics emerged, and therefore no revisions were made to the topic list. The interviews took approximately 60 min and took place at the patient's home to ensure a safe environ-

ment. Prior to the interview, written informed consent of the patient was obtained, and the patients' characteristics were collected. The global impression of severity (PGI-S), a validated one-item questionnaire with a four-point Likert scale from normal to severe, was used to assess the subjective severity of symptoms (17).

The interview started by exploring patients' expectations about treatment in general by using the first open-ended question, "What do you expect from a treatment for SUI?" Then, the interviewer informed participants about the procedure and complications of MUS surgery and PBI, as shown in the Appendix A. A non-degradable polydimethylsiloxane bulking agent (Urolastic®; Urogyn BV Nijmegen, The Netherlands) used at the institute was described as the PBI treatment. Patients were not yet informed about the efficacy of the procedure to specifically perceive the patients' perceptions of the procedure and safety of the treatment. Using the second open-ended question, "Which factors would you take into account if you could choose between PBI and MUS surgery?", the decision-making factors were explored when choosing between PBI and MUS surgery. The topic list was modified when new factors emerged. After the decision factors had been explored, the participants were informed about the efficacy of the treatment: 70% and 90% for PBI and MUS surgery, respectively (7, 11). The efficacy was defined as subjective cure: no symptoms of urine leakage during laughing, sneezing, coughing and physical exercise. It was mentioned that the long-term efficacy of PBI was unknown. The interview evaluated how the difference in efficacy influenced the women's treatment preference. In addition, patients' perspectives on MUS surgery in a daycare setting performed under local analgesia with combination sedation were explored. Third, the women's opinions about PBI as a primary treatment option were explored: "Would you consider PBI a primary treatment option?"

At the end of the interview, the interviewer gave a summary of the interview, which the participant could correct or complete.

**Data analysis**

All interviews were audiotaped and transcribed verbatim by the interviewer. The data were analyzed by two researchers who worked independently [FC; ZS] with the help of the MaxQdA12 software package. Deductive content analysis was used for pre-determined decision factors, and inductive content analysis was used to identify additional decision factors from the remaining narratives (22). Thematic analysis was done as follows (23, 24): 1. Interviews were read line by line and the decision factors were marked (open coding) (25). 2. The relationship of the codes was identified by categories and subcategories by means of constant comparison (axial coding) (26, 27). 3. The categories were combined with an iterative process and domains developed (selective coding) (26). The participants received feedback on the study findings.

## RESULTS

From November 2015 until July 2016, 33 women were approached for participation, and 11 women declined. Two patients were excluded from the study by purposive sampling because the patients had minimal complaints of SUI and this group of patients was already overexposed. The major reason for refusing participation was private matters; one woman indicated that she could not express herself properly. After interviewing 20 women, no new treatment decision factors were observed in three consecutive interviews, meaning data saturation had been reached and therefore no new women were approached for participation. The patient characteristics in Table 1 show the variety in age, cultural and educational background, duration of incontinence symptoms and subjective severity of incontinence symptoms (PGI-S).

**Table 1.** Patient characteristics

| Characteristic | N=20 |
|---|---|
| Age in years *median (range)* | 49 (23-88) |
| Duration of symptoms in months *median (range)* | 60 (6-964) |
| Use of anti-incontinence material *n (%)* | 15 (75) |
| Previous therapy for SUI *n (%)* | |
| None | 1 (5) |
| PFMT | 18 (90) |
| Unknown | 1 (5) |
| Sandvik severity scale* *n (%)* | |
| Mild | 0 |
| Moderate | 10 (50) |
| Severe | 10 (50) |
| PGI-S ** *n (%)* | |
| Normal | 0 |
| Mild | 11 (55) |
| Moderate | 5 (25) |
| Severe | 4 (20) |
| Etnicity *n (%)* | |
| Dutch | 17 (85) |
| Chinese | 1 (5) |
| Colombian | 1 (5) |
| Belgium | 1 (5) |

**Table 1.** *(Continued)*

| Characteristic | N=20 |
|---|---|
| Education *n (%)* | |
| Primary school | 1 (5) |
| Secondary school | 14 (70) |
| University | 5 (25) |
| Marital status *n (%)* | |
| Married | 13 (65) |
| Living together | 2 (10) |
| Single | 1 (5) |
| Widow | 4 (20) |
| Profession *n (%)* | |
| Full-time | 2 (10) |
| Part-time | 9 (45) |
| Unemployed | 3 (15) |
| Retired | 6 (30) |
| Parity *median (range)* | 2 (0-4) |
| Premenopausal *n (%)* | 11 (65) |
| Sexual active *n (%)* | 12 (60) |

* Sandvik severity scale is a validated index that scores the severity of urinary incontinence by multiplying the outcome points of two questions with regards to the frequency and amount of urinary loss. **: PGI-S: patients global impression of improvement is a validated scale to assess the patients 'subjective severity of urinary tract conditions.



### Treatment decision factors

Sixteen treatment decision factors, categorized in five domains, determined the patients' treatment preference between PBI and MUS surgery (Figure 1). Predetermined treatment decision factors from the topic list were all categorized in domain 'procedural factors.' Sexual function was deleted as a treatment decision factor because this was a factor related to undergoing treatment in general and did not discriminate between PBI and MUS surgery. After data analysis, ten new treatment decision factors and four new domains were identified. The top three most mentioned decision factors of the largest domains are described in the text. Table 2 shows illustrative quotations of reasons to opt for PBI or MUS surgery or to be indecisive.

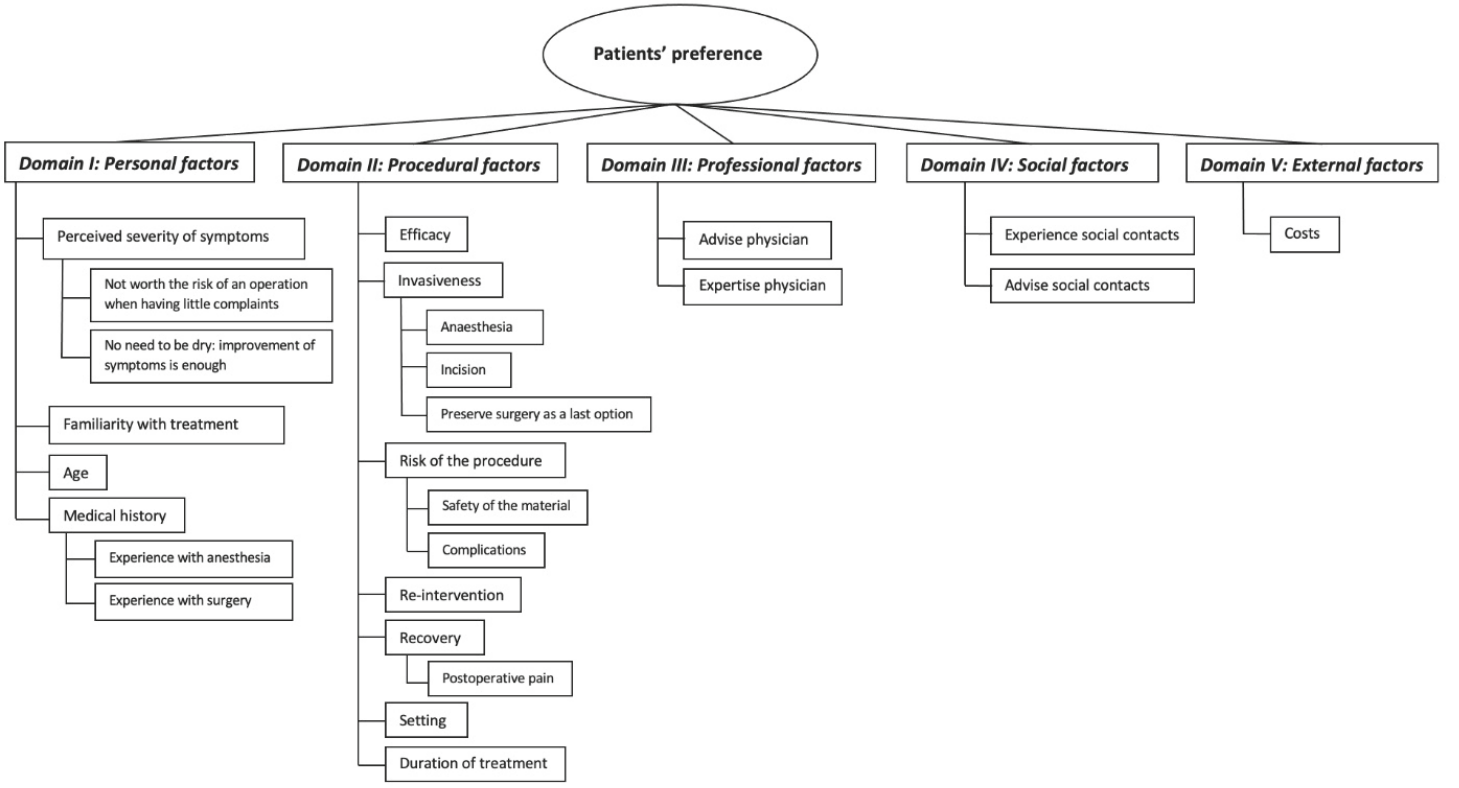


Figure 1. Code tree of domains and treatment decision factors

**Table 2.** Selected illustrative quotations

| Treatment preference | Treatment-decision factor | Quotation |
|---|---|---|
| **Preference for PBI therapy** | Having little complaints | *"I think I would not even consider the tape [refers to MUS-surgery], because I think it still does not outweigh the problems I have at this moment...the operation may be more efficacious, but that does not pursue me to undergo surgery"* (P10, 40 years) |
| | No need to be dry | *"I'm not like: I should be dry until the last drop. That is not a goal for me...So, then I still prefer the bulkinjection, because when you have improvement* [refers to symptoms of SUI] *it can be acceptable for everyday life"* (P5, 41 years) |
| | Preserve surgery as a last option | *"If it does not work* [refers to PBI]*, you can still choose the operation"* (P9, 47 years) |
| | Safety of the material | *"I would not dare* [refers to MUS-surgery]*, because you quickly hit something... and then those incisions..with all that scar tissue... just the idea that this tape can never be removed...So I would go for the bulkinjection"* (P16, 34 years) |
| | Avoid anesthesia | "*If I had to choose now, I would choose the bulk injection, but that is due to the fact that the operation is through an epidural or general anesthesia"* (P7, 23 years) |
| | Avoid incision | *"I would still prefer the bulkinjection, purely because they do not have to cut, I'm always afraid they hit things.* (P9, 47 years) |
| | Less invasive | *"The bulkinjection is more convenient. And less heavy. There are people who go to clinics to fill up certain things , well...this reminds me a bit of that"* (P1, 50 years) *"Although is less effective, I would still try this first* [refers to PBI] *because it is less invasive"* (P4, 37 years) |

**Table 2.** *(Continued)*

| Treatment preference | Treatment-decision factor | Quotation |
|---|---|---|
| **Preference for MUS-surgery** | Familiarity with treatment | *"I think the bulkinjections are scary...I don't know, maybe because you have heard little about it"* (P13, 71 years) |
| | Efficacy | *"The most important thing for me is it must be efficacious"* (P20, 48 years) |
| | Safety of the material | *"Sounds more chemical and scarier* [refers to PBI]*...imagine it's leaking or so...what can happen? What are the risks? Can it move? Could it be that your body does not accept it? That is will be expose itself? Can it get into your bladder? That kind of uncertainties"* (P4, 37 years) |
| | Avoid local analgesia | *"I think I would go for the operation, because then I am not awake* [refers to general anesthesia]*"* (P18, 86 years) |
| | Re-intervention | *"If the chance is 15% that you have to still must undergo anesthesia anyhow* [refers to excision of PBI]*, perhaps I would say, I will do the operation immediately"* (P14, 32 years) |
| | Experience social contacts | |
| | Expertise physician | *"I think I would choose the operation, because it is more effecious and there is more experience with the operation. But I would talk to my husband about it."* (P6,55 years) |
| **Indecisive** | Age | *"They do not have any experience with this* [refers to PBI] *in older women, so I think that is a risk to take. The injections seems painful. With an operation you don't feel anything, that is beneficial. But then afterwards...*[refers to recovery]*. And one women I know has been operated on twice, but is still as incontinent as before, so it didn't help. Why should I take that risk at my age?"* (P17, 88 years) |
| | Advise physician | *"I don't know...I will wait what the doctor tells me, I will wait for their advice."* (P2, 82 years) |

This table shows patients quotations that reflects the patients motives to prefer PBI treatment, MUS-surgery or be indecisive

**Domain I personal factors:** The patients' perceived severity of symptoms influenced the treatment preference. Women opted for PBI even if it would be less effective if they considered their symptoms not severe enough to undergo surgery or when they intended to achieve a reduction of symptoms rather can complete cure of incontinence.

Especially older patients mentioned age as a reason to prefer PBI over MUS surgery because they intended to avoid general or spinal anesthesia. On the other hand, also older women expressed fear of silicon-induced complications.

Finally, the familiarity of the treatment was a major factor influencing patient preference. MUS surgery was considered a well-known procedure, but PBI treatment was unfamiliar to the patients. Lack of confidence about PBI treatment tended to arise from unfamiliarity and was therefore a decision factor for opting for MUS surgery.



**Domain II procedural factors:** The minimally invasive characteristic was a repeated decision factor for choosing PBI. Although surgery had a higher success rate, some patients were keen to try the least invasive procedure first and reserve surgery as the last option. When further exploring the term 'invasiveness,' patients valued 'incision' and 'anesthesia' as the most incriminating factors. An incision was considered a risk factor for infection, bleeding and extensive fibrosis and was often dominant in patients' trade-off of treatment decision factors. The preference for type of anesthesia was very personal and based on previous experiences or fear of complications. Although local analgesia was generally perceived as appealing and a reason to choose PBI, one woman preferred MUS surgery because of previous painful experiences with local analgesia. When MUS surgery was offered as a procedure under local analgesia with sedation, most women perceived this to be a preferred setting, but only one woman who preferred PBI switched her preference to MUS surgery. Women who did consider local analgesia not beneficial had different reasons for this. Either women were too anxious about the pain during the procedure or anxious about being awake during the procedure, or they still considered the sedation a disadvantage. Finally, for some women the type of anesthesia was just not important in their treatment decision-making. The risk of the procedure and especially the safety of the material influenced the patient treatment preference. With respect to PBI, women worried about 'injecting something' because the substance could be resorbed, migrate or cause a foreign body reaction. Many questions and thoughts arose concerning the safety of the PBI material: "it sounds chemical and more scary." "Can it leak like silicone breasts?" "Can it be carcinogenic?" With respect to MUS surgery, women worried about fibrosis, infection, persistent pain or the inability to remove the whole sling.

Finally, the efficacy was a treatment decision factor. Table 3 reflects the treatment preference in relation to patients' age and severity of symptoms before and after informing them about the efficacy. One patient switched her preference from PBI

to MUS surgery after being informed about the difference in efficacy. Two patients first preferred PBI, but became indecisive after receiving information on efficacy. Two patients were indecisive, but afterwards preferred MUS surgery. Six patients still preferred PBI therapy, although they knew it was less effective. Seven patients preferred MUS surgery before and after informing them about the efficacy rates.

**Table 3. Hypothetical treatment preference related to the efficacy**

| Treatment preference | Before information on efficacy | After information on efficacy | PGI-S*ǀ | Ageǀ *median (range)* |
|---|---|---|---|---|
| PBI *n (%)* | 10 (50) | 6 (30) | Mild: 5<br>Moderate: 1 | 38 (23-47) |
| MUS-Surgery *n (%)* | 7 (35) | 11 (55) | Mild: 5<br>Moderate: 3<br>Severe: 3 | 55 ( 24-86) |
| Indecisive *n (%)* | 3 (15) | 3 ( 15) | Mild: 1<br>Moderate: 1<br>Severe: 1 | 82 (50-88) |

This table shows the number and percentage of patients that preferred PBI treatment, MUS-surgery or were indecisive before and after informing them about the efficacy of PBI treatment and MUS-surgery.
*: PGI-S: patients global impression of improvement is a validated scale to assess the patients'subjective severity of urinary tract conditions
ǀ : PGI-S and age presented in the table reflects the population of patients after information on efficacy

Patients found the outpatient setting, less postoperative pain and quicker recovery of PBI beneficial, but these factors were less dominant in treatment decision making. Also, when MUS surgery was presented as day-care ambulant treatment, this was found appealing, but was not decisive in their treatment decision-making.

**Domain III professional factors:** The advice and expertise of the physician were taken into account when choosing between PBI and MUS surgery. Especially older and indecisive women attached great value to advice from physicians. Women assumed that physicians were more experienced performing the MUS procedure than PBI and therefore expected a better outcome from MUS surgery.

**Domain IV social factors:** Especially experiences from other patients, but also advice from social contacts and family contributed to the patients' preference.

**Domain V external factors:** One woman enquired about the reimbursement and possible costs of the treatments.

**General expectation concerning treatment**

Regarding SUI treatment expectations, women believed 'becoming dry' was wishful thinking. As long as the remaining incontinence did not involve more than drops requiring one pad a day, or using small pads instead of large ones, they were satisfied. They accepted the consequences of giving birth and increasing age and did not expect that treatment could completely cure their incontinence symptoms. Other women expected to achieve more personal goals such as "playing field hockey with the children." A minority of the women said that they would not accept any urine loss after treatment.

**Perspective on PBI as a primary treatment option**

Regardless of the patients' treatment preferences, the lower efficacy of PBI treatment did not prevent them from believing that PBI should be offered as a primary treatment option. Women indicated that physicians should inform women about all possible treatment options, including PBI treatment, so they can carefully weigh the benefits and disadvantages of both treatments and make a well-informed decision. One woman indicated that, if she had more influence in decision-making, she would be more confident during her treatment. Another woman added that the physician's advice was a must.



## DISCUSSION

This study shows that patients with primary SUI consider PBI a valuable alternative treatment option even though it has lower cure rates compared with MUS surgery performed under general or spinal anesthesia. Second, patients indicated that PBI should be incorporated in shared decision-making and offered to all women with SUI.

In the counseling process for SUI treatment, attention mainly focuses on procedural factors such as the chance of cure, type of anesthesia, setting and recovery. However, this study shows that patients also take into account personal, professional, social and external factors when making a treatment decision for PBI or MUS surgery. Regardless of the chance of cure, the patients' preference for PBI or MUS surgery was strongly based on aversions to or concerns about the treatment method (respectively injection or incision) or the safety of the used material (respectively silicon or mesh). For example, some patients just disliked the idea of injections. On the other hand, safety issues regarding mesh was a decision factor for choosing PBI.

A major decision factor for choosing PBI was its minimally invasive character. Although MUS surgery is generally known as a minimally invasive procedure, some patients preferred PBI because they considered general or spinal anesthesia or the incision for MUS surgery too invasive. PBI treatment was found an appealing intermediate

option between conservative management and MUS surgery. Therefore, some patients wanted to reserve the most invasive procedure (MUS surgery) as the last treatment option, a phenomenon that was also described in a qualitative study by Milne *et al*. comparing conservative treatment versus surgery (28). Therefore, patients do not always prefer the treatment with the highest cure rate. This is supported by Petrou *et al.* who showed that patients prefer injectable therapy over tension-free vaginal tape surgery with a mean success rate as low as 34% (15).

Major decision factors involved in patients preferring MUS surgery were: the higher chance of cure, a one-session procedure, the familiarity with the treatment and safety concerns about PBI treatment. A qualitative study on patients' treatment preferences in women with pelvic floor disorders also reported that women with SUI want to have the treatment with the highest chance of long-term success, even if it is more invasive (29).

The patients' general expectations of treatment were the hope of achieving improvement of their symptoms, and only a few expected a complete cure. Moreover, women indicated having specific treatment goals, such as 'playing field hockey with my children again.' This is in line with other studies showing that treatment goals for patients with urinary incontinence are very personal and subjective (30–34). Therefore, even if PBI cure rates were significantly lower cure than for mid-urethral sling procedures, it cannot be concluded that PBI would not meet patients' treatment goals.

In this qualitative design, there are several uncertainties concerning the generalizability of the results. First, the results are not applicable for women who have recurrent SUIs after MUS surgery, as we excluded those women from this study. We purposely chose to include treatment-naive women to prevent influences of previous experiences on their perception. Second, the success rates and re-intervention rates mentioned by the interviewer are hypothetical and could be different from daily practice counseling. With respect to PBI, we used a 15% chance for both the re-injection rate and excision rate based on outcomes from clinical studies of a non-degradable polydimethylsiloxane bulking agent (11, 35). However, these re-intervention rates can differ significantly among different bulking agents. For example, the re-injection rate of the urethral bulking agent polyacrylamide hydrogel (PAHG) can be up to 35% (36). Since re-intervention was a decision factor for choosing MUS surgery, the differences in re-injection percentages of the different bulking agents could have influenced the women's preferences. Third, although data saturation for decision factors occurred, the sample size was small considering the wide range of patients with SUI. So, it might be that some patient characteristics have been underexposed, despite the fact that purposive sampling was used. For example, not all ethnicities were represented, and cultural factors may not have been identified. This effect might be minimal since a systematic review showed similar management strategies for urinary incontinence

among different racial groups. However, PBI was not evaluated in this systematic review (31). Fourth, we did not share details about the time-dependent characteristics of the efficacy of both interventions. Finally, an interview is a snapshot of women's perspectives, and their perspectives may change over time.

A strength of the study, by using a qualitative design, is that not only subtle distinctions of interpretations can be made, but also the broad spectrum of the patients' perspectives is highlighted. To structure the patient perspectives, domains were used to categorize the treatment decision factors. The layout of categorization (personal, procedural, professional, social and external domains) is reported in other studies (37, 38).



PBI treatment was introduced as a promising alternative treatment option for SUI. However, because of safety issues, high re-injection rates and the lack of durable results, it is not widely accepted as a valuable treatment option. Although a systematic review including 26 cohort studies of two currently used bulk materials shows subjective success rates ranging from 66 to 89.7% and objective success rates ranging from 25.4–73.3% at 12-month follow-up, randomized controlled trials with MUS surgery are missing (39). As a consequence of the lack of evidence, the precise indication for PBI is still unclear. This study shows that patients would consider PBI a primary option when a cure rate of 70% after 1 year is achieved. This outcome is an argument for comparable studies to determine whether current bulk materials meet this level of success. One meta-analysis that compared PBI with open surgery showed significantly inferior results for PBI regarding objective cure; however, subjective outcomes were not significantly different (14). Future studies therefore should include both subjective and objective outcomes.

This study shows that patients have different reasons to consider PBI as a primary treatment option compared with MUS surgery. In addition, patients indicated that PBI should be offered to all women with SUI. Comparable studies are however needed to objectify whether current bulking agents do meet cure rates as used in this study and to determine the precise indication for PBI treatment. Since the patient has gained a participant role when it comes to healthcare decisions, one should still identify the patient's perspective when tailoring treatment for SUI. The treatment decision factors identified in our study will help physicians to address the correct items in the discussion with the patient about the treatment of choice.

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## CONFLICT OF INTERESTS

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## APPENDIX A: Treatment description of PBI and MUS surgery

The procedure and complications of PBI and MUS surgery were explained in detail by the interviewer using an information leaflet, but withholding information about the efficacy of the treatment options. MUS surgery was described as an operation that required general or spinal anesthesia and hospital admission for 1 or 2 days. Postoperative analgesia was usually necessary. The recovery period was described as 1 week. Postoperative lifestyle advice (such as no lifting, no cycling and no physical exercise) was applicable for 4–6 weeks. Possible complications involved: urinary retention, urgency incontinence, urinary tract infection, hemorrhage during or after surgery, wound infection, persistent pain, dyspareunia and exposure of the sling through the vaginal wall. The PBI that was presented was a non-degradable polydimethylsiloxane bulking agent. PBI was described as a procedure under local analgesia injecting a non-absorbable silicon substance at four locations around the urethra. The procedure was performed in an outpatient setting, and hospital admission was not necessary. The procedure time was set at 20 min. Postoperative analgesia was seldom indicated, and the recovery was 1 to 2 days. Postoperative lifestyle changes as described in MUS surgery were also applicable to women treated with a PBI. The risk of having to undergo a re-injection of two extra silicon deposits in case of recurrent SUI was set at 15%. Possible complications involved: urinary retention, urgency incontinence, urinary tract infection, wound infection, exposure or expulsion of the bulking agent, persistent pain and dyspareunia. The risk of having to remove one or more silicon deposits because of the aforementioned complications was set at 15%. Excision of one or more deposits could indicate spinal or general anesthesia and hospital admission.

# Chapter 3

# How cure rates drive patients' preference for urethral bulking agent or mid-urethral sling surgery as therapy for stress urinary incontinence

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## ABSTRACT

### Aims

To assess the patients' median-accepted threshold of cure rate for urethral bulking agent (UBA) treatment compared to mid-urethral sling (MUS) surgery for treatment of female stress urinary incontinence (SUI). Secondly, to determine the correlation between treatment trade-off point and patient characteristics.

### Methods

Women older than 18 years, with predominant SUI, seeking treatment, underwent a structured interview. The treatment trade-off point was determined in scenario one: UBA vs transobturator standard MUS surgery (SMUS) performed under general/spinal anesthesia with one-night hospital stay, and scenario 2: UBA compared to single-incision MUS surgery (SIMS) performed under local analgesia (with sedation) in a day-care setting. The treatment trade-off point was assessed by decreasing the cure rate of UBA from 85% to 10% with steps of 2% until the patient's treatment preference switched to SMUS/SIMS.

### Results

One hundred and five patients were interviewed. Mean age was 52 years (SD, ±13.4). The median trade-off point for scenarios 1 and 2 was 79% (interquartile range [IQR]: 69, 85) and 85% (IQR: 71, 85), respectively. Patients with longer duration of SUI symptoms were willing to trade more efficacy to prefer UBA treatment.

### Conclusions

Patients with SUI are willing to trade a lower cure rate to prefer UBA over SMUS to avoid hospitalization and general anesthesia. When SIMS is performed in a daycare setting under local analgesia, the majority of patients with SUI are of the opinion that cure rates of UBA should be at least as high as SIMS to be worth considering. The treatment preference is not strongly correlated with the patients' characteristics.

## INTRODUCTION

Stress urinary incontinence (SUI) is a common condition that affects one out of three women (1). There are several options for the treatment of SUI available with varying cure rates and invasiveness. Mid-urethral sling surgery (MUS) is often the preferred surgical treatment, because it is associated with high cure rates accompanied with an acceptable safety profile. MUS surgery includes standard mid-urethral slings (SMUS), either by retropubic or transobturator approach, and single-incision mid-urethral slings (SIMS). SIMS are less invasive compared to SMUS and can therefore more easily be performed in an outpatient setting under local analgesia. Moreover, although SIMS are very different from each other, some have been evaluated in randomized controlled trials and shown to be associated with shorter operative time, less postoperative pain yet, and noninferior cure rates of 85% in comparison to transobturator tapes (TOT) (2,3).



Urethral bulking agents (UBA) are an alternative option to treat SUI and can be performed in an outpatient setting using local analgesia. This can be seen as potentially beneficial to patients compared to MUS surgery. In addition, the postprocedure lifestyle restrictions when using UBA are minimal, whereas in MUS surgery patients are advised to adjust physical activities until 4 weeks after surgery. UBA target SUI by injecting a bulk mass just below the mucosa resulting in approximation of the urethral walls and thus increased urethral compression. With a low complication rate of 0% to 5.7%, the safety profile seems to be better than MUS surgery (4,5). Variable clinical success rates of UBA of 50% to 89% after 1-year follow-up are reported (6-8). The National Institute for Health and Care Excellence and the European Association of Urology (EAU) guidelines recommend UBA to be used for short-term management of SUI if conservative management has failed. Both guidelines emphasize that multiple injections are required. In addition, the EAU states that UBA should not be offered in case a permanent cure is required (9). The indication of UBA is unclear, as it is used for mild SUI and at the same time seen as a last option when other treatments have failed, in patients with intrinsic sphincter deficiency or in patients with a contraindication for MUS surgery or general/regional anesthesia.

Studies on patients' preference for SUI treatment are essential to define the role of UBA therapy in treatment-decision making. According to one qualitative study, patients with SUI prefer to have the treatment with the highest success rate (10), whereas another study reports that patients with SUI prefer a procedure with a low risk of complications and accept the accompanying lower success rate (11).

The objective of this preference study was to investigate the median-accepted threshold of cure for UBA when compared to SMUS and SIMS surgery. We hypothesized that patients are willing to trade cure in favor of UBA treatment over transobturator SMUS surgery, to avoid general or spinal anesthesia and overnight stay in the

hospital. When MUS surgery is be offered as a treatment under local analgesia with sedation performed in a daycare setting, referring to SIMS, we hypothesized that the median-accepted threshold of cure rate of UBA is higher. Second, we aimed to investigate whether patient characteristics correlate with the patient's preference.

## METHODS

A semiquantitative preference study with a treatment trade-off design was performed in two teaching hospitals in the Netherlands and one in South Africa. Ethical approval was required and approved by the Medical Ethical Committee of the participating hospitals.

The primary outcome was the patient's treatment trade-off point, being the threshold for cure rate at which the patient's preference switched from UBA to transobturator SMUS (scenario 1) and SIMS (scenario 2), respectively. Cure was considered to be present if the patient did not experience symptoms of urinary leakage during coughing, sneezing, laughing, or physical exercise. Secondary outcomes were, correlations between treatment trade-off point and patient characteristics including age, marital status, severity of symptoms, disease-specific quality of life, previous experience with anesthesia (general, spinal, and local), and previous MUS surgery.

### Recruitment and study design

Women older than 18 years with predominant SUI and seeking treatment were informed about the study by their gynecology and a subject information letter was handed out. Patients suffering from predominant urgency incontinence or patients who were unable to give informed consent were excluded from the study. Written informed consent and patient characteristics were obtained, whereafter an interview was planned. The face-to-face interview took place in the hospital and took about 30 minutes. If a patient was unable to conduct the interview face-to-face, the interview was conducted by telephone. The structured interviews were conducted by four Dutch, female medical students, who were extensively trained to perform these interviews and were supervised by the principal investigator of the participating hospitals.

The design of the interview was a treatment trade-off method, which has been successfully used in previous patient preference studies (12,13). In a treatment trade-off method, specific treatment characteristics of two treatment options (A and B) were changed, until the patient switched her preference from A to B. The point at which the patient switched their preference was defined as "trade-off point". Each patient participated in two trade-off scenarios, where the sequence of both trade-off

experiments was held constant; scenario 1, UBA compared to SMUS and scenario 2, UBA compared to SIMS.

**Trade-off experiment**

The first treatment trade-off scenario compared UBA with transobturator SMUS. Transobturator SMUS was presented as a treatment performed under spinal or general anesthesia in a hospital setting with one-night stay. UBA was presented as a treatment under local analgesia in an outpatient setting without hospital admission. First, a standardized description including images of both treatments including information on the procedure, setting, anesthesia, and complications were given to the patient (Appendix A). Adverse events of UBA that were presented, were: urinary tract infection, urinary retention, complaint of urgency, pain or uncomfortable feeling and exposure. No complication rates were given. The reinjection rate for UBA was set at 20%. The description did not included information on cure rates, because the primary outcome of the study was the median-accepted cure rate. Giving information on different cure rates regarding UBA and SMUS or SIMS, before the trade-off experiments, could have introduced bias. During the telephone interview, the patient was asked to have the description of the treatments in her hands to be able to read along with the verbal explanation of the interviewer. After explaining both treatment options, hypothetical cure rates for both treatments were set at 85% and the treatment preference and motive for treatment preference of the patient was assessed. The hypothetical cure rate for SMUS surgery was kept constant at 85% while cure rates for UBA treatment decreased from 85% towards 10% with steps of 2% until the patient's preference switched to SMUS surgery. Simultaneous visualization was offered by presenting the patient a pictograph which showed the varying success rates. The cure rate at which the patient switched from UBA to SMUS surgery was defined as the trade-off point and was registered by the interviewer, as well as the reason why the patients switched in preference was carefully registered.

The second treatment trade-off scenario compared UBA with SIMS. SIMS was presented as a treatment under local analgesia with sedation in a daycare setting. The same trade-off design as scenario 1 was used to determine the treatment trade-off point of scenario 2. The SIMS presented was an adjustable polypropylene mesh, fixated in the obturator membrane with anchors, and introduced with a helicopasser (Altis® Single Incision Sling System; Coloplast®; The Netherlands). Single-arm cohort studies show subjective and objective cure rates of 84% and 90%, respectively at 12-month follow-up, with durable results at 24-month follow-up (14, 15).

### Questionnaires

To assess symptom distress of urinary incontinence and its impact on daily life, the validated Dutch versions of the Urinary Distress Inventory (UDI-6) and the Incontinence Impact Questionnaire (IIQ-7) were used. UDI-6 scores include several urogenital symptoms namely: urgency, frequency, stress related urinary incontinence, and bulge feeling. For this study, we also looked solitary at the stress domain. IIQ-7 has a range from zero to 100, with higher scores indicating a more negative effect on health-related quality of life (IIQ). The severity of the symptoms was classified as mild, moderate, or severe according to the severity index by Sandvik.16 The Patient Global Impression of Severity (PGI-S) index was used to assess the perceived severity of incontinence symptoms on a 4-point Likert scale after treatment.

### Sample size and statistical analysis

As a rule of thumb, at least 10 patients were included for each variable that was used in the multivariable model. A sample of 105 patients was needed. Descriptive analysis was used to present the treatment trade-off point and the patients' motives for treatment preference. Correlations between the treatment trade-off point and continuous and ordinal data were analysed using the Spearman test. The Mann-Whitney U test and Kruskal-Wallis tests were used to assess significant differences of treatment trade-off point (not normally distributed) between unpaired groups. The Wilcoxon signed rank test were used to assess significant differences of treatment trade-off point (not normally distributed) between paired groups. Statistical analyses were performed using SPSS version 22 (IBM Corp, Armonk, NY). $P < 0.05$ was considered a threshold for statistically significance.

## RESULTS

From March 2017 to February 2018 a total of 105 patients were included and interviewed. Five patients were interviewed by telephone and 100 patients were interviewed face-to-face.

The patient characteristics are shown in Table 1. The mean age was 52 ± 13.4 (SD), median duration of SUI symptoms was 60 months, 30% considered their symptoms "severe" at the PGI-S, whereas 46% were scored severe on the Sandvik Severity Scale, and 10% had underwent previous MUS surgery.

**Table 1. Patient Characteristics**

| | | Total |
|---|---|---|
| | | N = 105 |
| Age, mean (SD) | | 52 (13.4) |
| Education* completed, n (%) | Lower education | 10 (9.6) |
| | Medium education | 73 (69.5) |
| | High education | 22 (21.0) |
| Work, n (%) | Working | 71 (67.7) |
| | Non-working | 34 (32.4) |
| Menstrual cycle, n (%) | Post-menopausal | 41 (39) |
| Parity, median (IQR) | | 2 (2, 3) |
| Sexually active, n (%) | | 68 (64.8) |
| Marital status** (%) | Co-habiting | 75 (71.4) |
| | Single | 29 (27.6) |
| Duration of symptoms (months), median (IQR) | | 60 (36, 132) |
| Sandvik Severity Scale, n (%) | Mild | 10 (9.5) |
| | Moderate | 47 (45) |
| | Severe | 48 (46) |
| PGI-S, n (%) | Normal | 12 (11.4) |
| | Mild | 24 (22.9) |
| | Moderate | 37 (35.2) |
| | Severe | 31 (29.5) |
| Treatment expectation, n (%) | Not completely dry | 18 (17.1) |
| | Completely dry | 86 (81.9) |
| IIQ-7 †, median (IQR) | | 43 (24, 57) |
| UDI-6 ‡, median (IQR) | | 38 (25, 46) |
| Previous treatment for SUI, n (%) | No | 40 (38.1) |
| | Yes, pelvic floor physiotherapy | 50 (47.6) |
| | Yes, MUS-surgery | 10 (9.6) |
| | Yes, UBA | 3 (2.9) |
| | Yes, pessary | 2 (2) |
| General anaesthesia, n (%) | No experience | 30 (28.6) |
| | Yes, good experience | 69 (65.7) |
| | Yes, bad experience | 6 (5.7) |

*Education: Lower education: pre-school and primary education, Medium education: secondary and vocational education, High education: academic education

** Cohabiting: Married and unmarried co-habiting, Single: single, widows and divorcees.

† IIQ-7: Incontinence Impact Questionnaire.

‡ UDI: Urogenital Distress Inventory.

The score in both UDI-6 as IIQ-7 has a range from 0 to 100, with higher scores indicating more distress caused by urogenital symptoms (UDI) or a more negative effect on health-related quality of life (IIQ).[22]

**Treatment trade-off experiment: scenario 1**

In scenario 1, UBA treatment was compared with transobturator SMUS performed under general anesthesia in a hospital setting with overnight stay. Figure 1 shows the distribution in trade-off for scenario 1. When a hypothetical cure rate of 85% for both SMUS and UBA was presented, 40 patients (38%) preferred SMUS surgery. The treatment trade-off point of the 105 patients varied between 10% and 85% with a median of 79% (interquartile range [IQR]: 69, 85), implying patients would trade 6% of cure rate to prefer UBA treatment over SMUS. Patients preferring UBA over SMUS (62%) were willing to trade a median cure rate of 14% (median trade-point of 71%; IQR: 60, 79).


**Figure 1.** Boxplot treatment trade-off point

**Treatment trade-off experiment: scenario 2**

In scenario 2, UBA treatment was compared with SIMS under local analgesia with sedation in a daycare setting. Figure 1 shows the distribution in trade-off for scenario 2. When a hypothetical cure rate of 85% for both SIMS and UBA was presented, 55 patients (52%) preferred SIMS surgery. The treatment trade-off point of the 105 patients varied between 10% and 85% with a median of 85% (IQR: 71, 85), implying patients were not willing to trade any cure. However, patients preferring UBA over SIMS (48%) were willing to trade a median cure rate of 16% (median trade-off point of 69%; IQR: 76, 79).

### Correlations patient characteristics and treatment trade-off point

A significant, but weak positive correlation was found for duration of symptoms (situation 1: P = 0.02, r = 0.22; situation 2: P = 0.049, r = 0.19), implying that patients with longer duration of SUI symptoms were willing to trade more cure rate to prefer UBA treatment. No correlations were found between age, severity of symptoms, disease-specific quality of life, previous MUS surgery or previous anesthesia, and the treatment trade-off point (Table 2). No significant differences in trade-off point were found between study patients in South Africa and the Netherlands.

**Table 2. Correlations between trade-off point and patient characteristics**

| | **Trade-off experiment 1** | **P-value** | **Trade-off experiment 2** | **P-value** |
|---|---|---|---|---|
| | Correlation coefficient | | Correlation coefficient | |
| Age | *r=0.17 | p=0.09 | *r=0.08 | p=0.40 |
| Duration of symptoms (months) | *r=0.22 | **p=0.02** | *r=0.19 | **p=0.049** |
| Sandvik Severity Scale | *r=0.14 | p=0.17 | *r=0.12 | p=0.21 |
| PGI-S | *r=0.11 | p=0.26 | *r=0.02 | p=0.84 |
| IIQ-7 | *r=0.15 | p=0.13 | *r=0.10 | p=0.30 |
| UDI-6 | *r=0.09 | p=0.39 | *r=0.03 | p=0.76 |
| Previous MUS-surgery *median (IQR)* | | p=0.29‡ | | p=0.90‡ |
| Surgery | 84 (74-85) | | 84 (68-85) | |
| No surgery | 79 (67-85) | | 85 (71-85) | |
| Previous General anaesthesia *median (IQR)* | | p=0.13# | | p=0.31# |
| No | 72 (56-85) | | 80 (57-85) | |
| Yes, good experience | 82 (69-85) | | 85 (71-85) | |
| Yes, bad experience | 79 (76-85) | | 85 (81-85) | |

*Spearman ‡ Mann Whitney U # Kruskal Wallis test

### Motivations behind treatment preference

Figure 2A and 2B show the variance and number of one or more motivations patients had behind treatment preference for MUS surgery and UBA treatment, respectively. Most mentioned reasons to prefer MUS surgery were: fear of silicones, one-off procedure, and unfamiliarity of UBA treatment. Most mentioned reasons to prefer UBA treatment were: minimal invasiveness, local analgesia, and quick recovery.

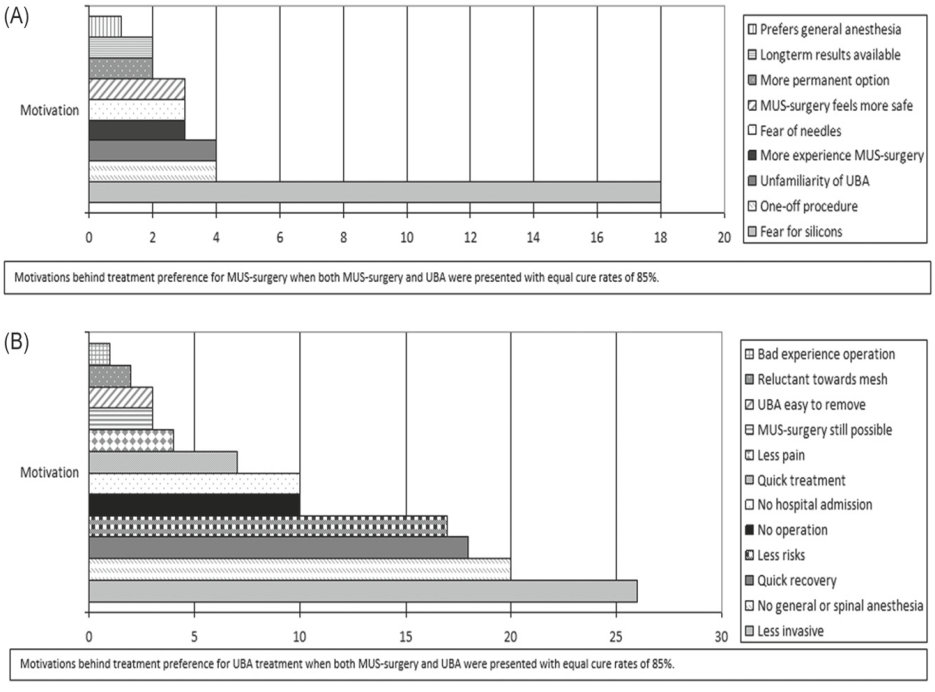


**Figure 2A and B.** A: Motivations behind preference for MUS surgery. B: Motivations behind preference for UBA treatment.

## DISCUSSION

This study shows that when cure rates of UBA treatment would be as high as transobturator SMUS, 62% of patients with SUI prefer UBA treatment. Patients are thereby willing to trade 6% of cure rate because of the minimally invasive aspect and use of local analgesia of UBA. When SIMS surgery is performed in a daycare setting under local analgesia, 48% of the patients with SUI prefer UBA and the majority of patients are not willing to trade any cure rate. Second, no strong correlations were found between the median-accepted threshold of cure rate and patients characteristics such as age, duration or severity of symptoms and previous failed MUS surgery.

The fact that patients are willing to trade cure for a less invasive procedure has been reported in previous studies (11,12). Petrou *et al* carried out a similar trade-off study and reported a mean acceptable cure rate of injectable therapy compared to surgery of 34% (11). The results from that study are difficult to compare to our data since it is unclear what the comparative surgical procedure was. In addition,

Petrou *et al* studied a smaller sample of patients, and in comparison to our study, their patients were older and had a higher incidence of failed treatment.
A remarkable result of our study is that, when UBA was presented hypothetically as effective as MUS surgery, 38% and 52% of the patients would still prefer SMUS and SIMS respectively, thereby taking into consideration the higher risk of complications. Patients preferring MUS surgery were concerned about the possible complications induced by silicones used in UBA polydimethylsiloxane. In addition, the considerable reinjection rate and the unfamiliarity with UBA were the most frequently mentioned reasons to prefer MUS surgery. Thus, apart from the invasiveness, type of anesthesia and setting, other motives are taken into account when selecting a treatment option for SUI. This is in keeping with the results of a qualitative interview study we performed, where we identified 16 treatment-decision factors influencing the patients preference for UBA or MUS surgery (18).



In our study, we did not find any strong correlations between patients characteristics and the preference for UBA or MUS surgery. Although patients with longer existing SUI symptoms were more likely to have a lower median-accepted threshold of cure rate, the correlation was weak ($r$ = 0.22 and $r$ = 0.19). Different correlations between patients characteristics and treatment preference for SUI have been described. Sullivan *et al* showed that younger, sexually active women, women having bothersome symptoms and a higher degree of pelvic organ prolapse with SUI desired surgical treatment more often as compared to conservative treatment (19). Schellart *et al* reported that younger women and single women accept lower cure rates of SIMS to avoid the postoperative groin pain associated with TOT (12). Regardless of the patients› characteristics, the patient›s treatment preference should be discussed when making treatment decisions for SUI.

There are possible limitations to this study. First, four different interviewers conducted the interviews which increases the intra-interviewer variability and contributes to the variance in the outcome. However, the format of the interview was standardized to minimize variances. Second, telephone interviews required patients to have a certain level of abstract ability to understand the experiment. The vast majority of the interviews were however conducted face-to-face. Third, physicians state different things about surgical options for SUI, and variation in the received information may have affected the responses to the interview. Finally, the information about the UBA was derived from polydimethylsiloxane Urolastic data, which is the UBA that is clinically used in the participating centers. Reintervention and complication rates are different from other existing UBAs and as a consequence, the preference for an alternative UBA could result in different findings (20).

Different surgical treatment options for SUI are available including MUS surgery, autologous fascia sling, Burch colposuspension and urethral bulking agents. The avail-

ability of multiple treatment options results in practice variation (17). MUS surgery is often the preferred treatment option, however, the AUA (American Urological Association) and SUFU (Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction) recommend to individualize the choice of intervention based on the patients' goals and expectations (21). Consensus of the EAU and the European Urogynecological Association also state to evaluate all available treatment options (22). Studies on patient's preferences regarding different treatment options for SUI are therefore crucial to optimize future trials and guidelines. For example, Tincello *et al* addressed the discrepancy between the surgeons› and patients› view on treatment of recurrent SUI after failed MUS surgery (23). While surgeons have most faith in a repeat MUS operation, patients feel reluctant to undergo the same procedure and are more keen on trying other treatment options. Our preference study shows that cure rates of UBA must be at least 79% to be an attractive alternative treatment for patients. Randomized trials comparing UBA with MUS surgery are needed to determine if UBA treatment achieves cure rates of 79% or higher. Cohort studies of bulking agent Urolastic report results lower to this threshold with subjective and objective cure rates of 56% to 68% and 59% to 65%, respectively, after 6- and 12-month follow-up (4,7,27). A systematic review of other bulking agents show on the other hand subjective and objective success rates up to 89% and 73% (8).

There is no worldwide consensus about the exact place of UBA in current treatment protocols. Most settings preserves UBA as a last-line therapy, but there are settings where UBA is offered as a first line therapy. Over the last years there is development in UBA therapy. New products have been introduced that involve larger, non-degradable particles and thus less migration, and potentially, higher cure rates. In the near future, cure rates of UBA may come close to the cure rates of SMUS. Therefore, this trade-off experiment is very relevant. This study is timeless and may be valuable in future years when possibly new UBA therapies are available with different cure rates.

## CONCLUSION

Patients with SUI are willing to trade a small amount of cure rate to prefer UBA over SMUS to avoid hospitalization and general anesthesia. When SIMS is performed in a daycare setting under local analgesia, the majority of patients with SUI find that cure rates of UBA must be at least as high as SIMS to be worth considering. The treatment preference is not strongly correlated with the patients' characteristics.

## CONFLICT OF INTERESTS

Jan-Paul W.R. Roovers reports grants from Urogyn BV and Coloplast. Fenne M. Casteleijn, Stephen Jeffrey, Rosa Enklaar, Ikram El Bouyahyaoui and Sandra E. Zwolsman have nothing to declare.

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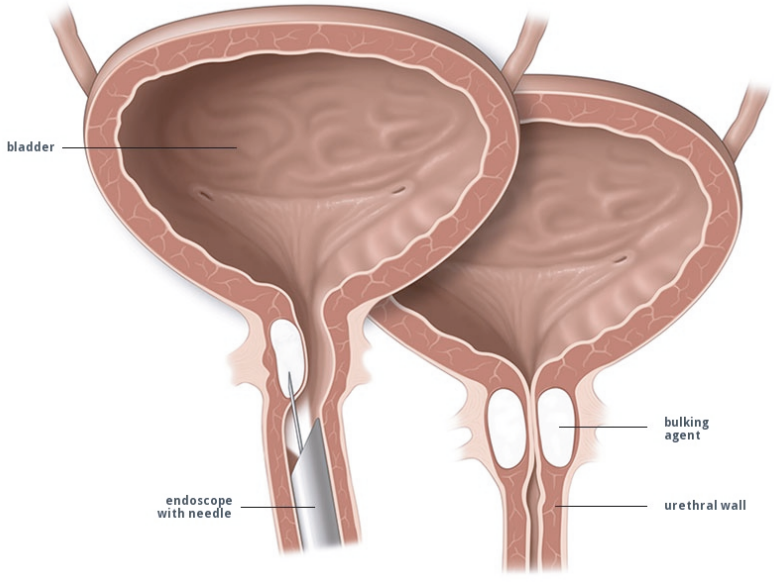
## APPENDIX A. Descriptive of treatment

### Treatment with urethral bulking agents




*Procedure*

This treatment consists of a substance that will be injected in the urethra wall. This treatment will take place in an ambulatory setting under local analgesia. So you do not have to undergo general anesthesia. After analgesia the bladder will be filled through a urine catheter. Then, the agent will be injected at four different places. The overall procedure takes twenty minutes. In general people will not experience any pain back home. Some will have a bruised sensation for several days.

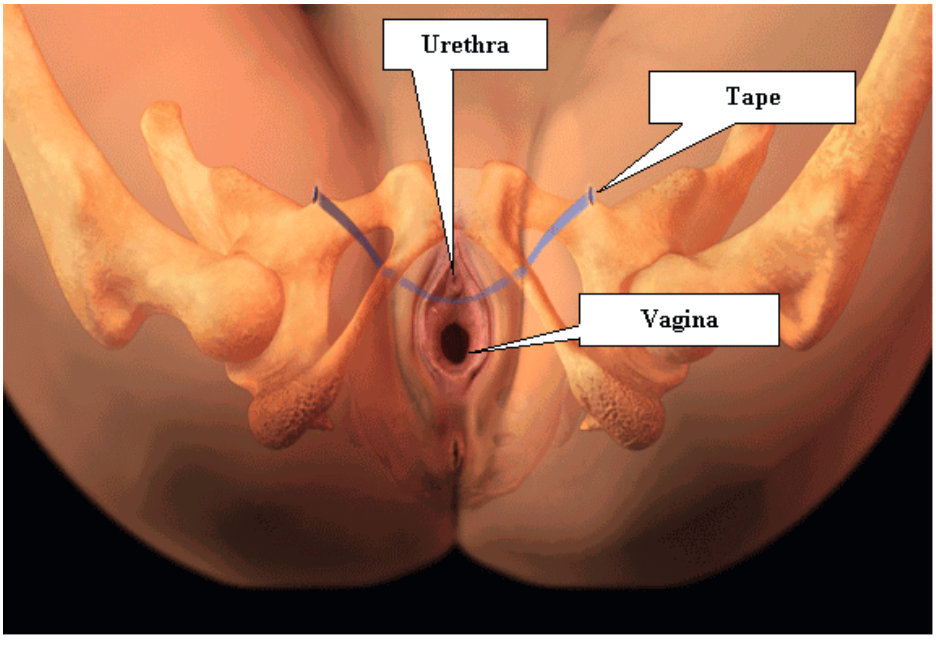
The treatment is supposed to be one-off in principle. But, one in five patients will not have a successful treatment and will need a second visit to inject more of the agent in two places.

*Potential Negative effects*

- Urinary tract infections
- Unable to have a complete urination. This usually happens directly after the procedure. In that case, you can get a urinary catheter. This usually takes one to several days.
- Complaints of the urge to urinate.
- Pain or an uncomfortable feeling (sometimes also during intercourse)

- The agent shows through the vaginal wall. Sometimes the agent can appear/come through the vaginal wall. This will not necessarily give complaints. When it does give complaints, the agent needs to be removed. Sometimes it may be removed at the outpatient clinic, but usually this will be done in a surgical theatre.

**Treatment with tension free vaginal tape (sling) surgery**




*Standard mid-urethral sling (SMUS) surgery*

**Procedure**

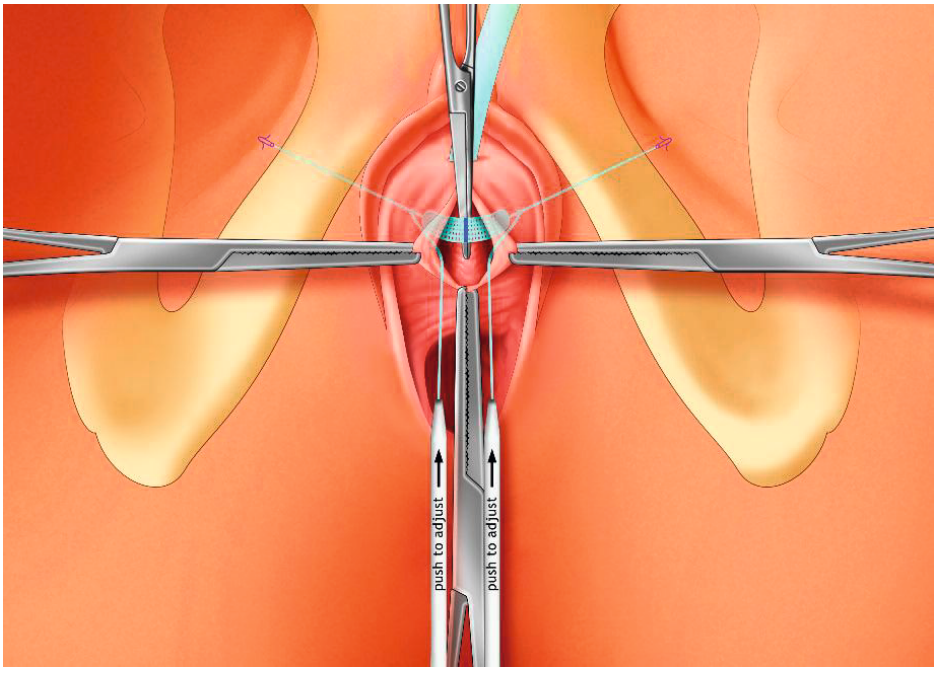
This is the most common surgical treatment for stress urinary incontinence. In this procedure, a tape of synthetic mesh(sling) is placed under the urethra to lift and support the urethra. This surgery requires three small incisions: one in the vagina and two in the upper legs. The procedure is done in an operating theatre under general anesthetic or regional anesthetic (spinal).

**Potential Negative effects**

- Postoperative groin pain (persistent)
- Urinary tract infections
- Damage of the bladder

- Bleeding during surgery
- Wound infection
- Unable to have a complete urination. This usually happens directly after the procedure. In that case, you can get a urinary catheter. This usually takes one to several days
- Complaints of the urge to urinate
- Pain or an uncomfortable feeling (sometimes also during intercourse)

**Single-incision minisling (SIMS) surgery**




**Procedure**

In this procedure, a tape of synthetic mesh(sling) is placed under the urethra to lift and support the urethra. This surgery is almost the same as the standard mid-urethral sling, only the sling is shorter. Because it is shorter, the sling does not perforate the muscles and patients do not have postoperative groin pain. The surgery requires one small incision in the vagina. The procedure is done in an outpatient setting under local analgesia (with sedation).

**Potential Negative effects**

- Urinary tract infections
- Extra bleeding during surgery
- Damage of the bladder
- Wound infection
- Unable to have a complete urination. This usually happens directly after the procedure. In that case, you can get a urinary catheter. This usually takes one to several days
- Complaints of the urge to urinate
- Pain or an uncomfortable feeling (sometimes also during intercourse)

# Chapter 4

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

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## ABSTRACT

### Aims

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

### Methods

In a cross-sectional design, patients treated with PDMS-U 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 reinterventions.

### Results

About 110 patients participated, 87 revisited the hospital. Median follow-up was 25 months (interquartile range: 14;35 months). Patients' satisfaction rate was 51%. Subjective 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. Reintervention rate of reinjection and excision of bulk material was 6% and 18.0%, respectively. Objective cure significantly worsened during time-after-treatment (P = <.05).

### Conclusions

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 (QoL) 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 (eg, 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 noninvasive, ambulatory treatment that involves injecting a bulk material transurethral or periurethral, 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). Periurethral injection therapy polydimethylsiloxane Urolastic (PDMS-U) (Urogyn BV Nijmegen, The Netherlands) is one of the latest developed bulking agents and consists of a smooth, nondegradable 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 periurethral at 2, 5, 7, and 10 O'clock at the mid-urethral level, without cystoscopic control.

From 2011, multiple hospitals have included PDMS-U a 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 (8,9,10). 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 reinterventions, 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.

## METHODS

A multicenter, cross-sectional study was performed in four experienced centers. Site specific information is shown in Appendix A. To evaluate the influence of a learning curve, only centers 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 centers.

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 reinterventions. In case patients were unable to revisit the hospital, a paper questionnaire was send to their homes. Patient characteristics, complications, and reinterventions 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): "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?" (15). 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 reinterventions, 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 (16,17). 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. Reintervention 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 posttreatment.

### 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 enrollment.

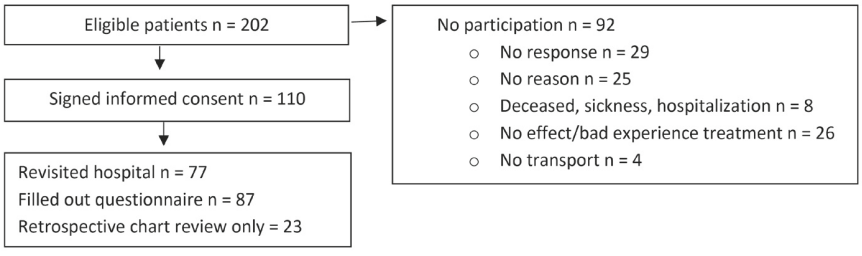


**Figure 1. Flowchart patient recruitment**

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 A shows overall outcomes and outcomes per study site.

**Table 1. Patient and procedural characteristics**

| | **Total 110** | |
|---|---|---|
| | N | % |
| Age *mean* (SD*) | 64 (13) | |
| BMI[ɬ] *mean* (SD) | 27 (5) | |
| Parity *median* (IQR^) | 2 (2;3) | |
| Smoker at time of procedure | 12 | 11 |
| Postmenopausal status | 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 |
| Preoperative pad use per day *mean* (SD) | 3 (2) | |
| Sexually active | 59 | 54 |
| Previous treatment for SUI^ǂ | | |
| No treatment | 23 | 21 |
| Pelvic floor muscle therapy | 45 | 41 |
| Sub-urethral sling surgery (≥1) | 29 | 26 |
| Injection therapy bulking agent | 5 | 5 |
| Burch colposuspension | 3 | 3 |
| Other [ɣ] | 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) | |
| 0-12 months | 18 | 21 |

**Table 1.** *(Continued)*

| | Total 110 | |
|---|---|---|
| | N | % |
| 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 | | |
| Droplets | 10 | 11 |
| More than droplets | 76 | 87 |

*SD: Standard Deviation, BMI: Body Mass Index, ^IQR: Interquartile Range, Other: Anterior colporrhaphy (n=4), laser (n=2), myoblasts injection (n=2), pessary (n=1), estrogen (n=1), SUI: Stress Urinary Incontinence. Total number is n=119, due to the fact that some patients have had multiple therapies

### 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).

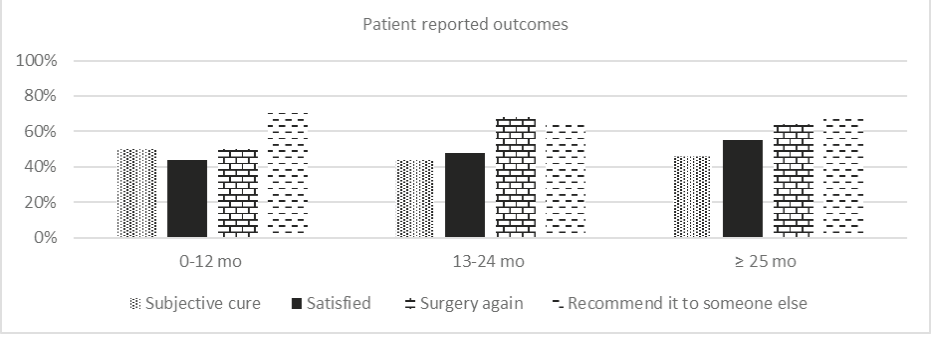


**Figure 2. Patients' satisfaction and subjective cure following time-after-treatment.** Subjective cure is defined as: answers corresponding to "very much better" or "much better" on the Patient Global Impression of Improvement. Satisfied is defined as: answers corresponding to "very satisfied" or "satisfied" 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 reinterventions**

Perprocedural complications did not occur. Table 2 represents the postprocedural complications and reinterventions. 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 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 hematuria. 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 hematuria (n = 1).

**Table 2.** Complications and reinterventions

| 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‡ | 16 | 14.5 |
| Dyspareunia | 16 | 14.5 |
| Uncomfortable hard feeling vagina[γ] | 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 ‖ | 5 | 25 |
| Re-injection | 7 | 6.3 |
| MUS-operation after Urolastic treatment | 6 | 5.5 |
| Other re-intervention[3] | 3 | 2.7 |

Overview of complications and re-interventions.

‡ Pain urogenital area > 2 weeks after treatment, other than dyspareunia

[γ] An uncomfortable feeling of the presence of bulk material during daily activities without pain

‖ Other location of excision: bladder (n=2), para-urethral left (n=2), para-urethral left and right (n=1)

[3] rectus fascia sling (n=1), PMFT (n=1), excision hematoma (n=1)

Prevalence of reintervention including reinjection, excision, or other reinterventions was 33% (n = 36). Reinjection of PDMS-U was done in seven patients (6%). Median time-after-treatment of reinjection was 4 months (range: 0 days to 18 months). In three patients the reinjection was performed directly after the initial procedure. Five of the seven patients that had undergone reinjection 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 anesthesia.

**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-6ᵞ 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-7ǂ 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.

*SD: Standard deviation

ᵞ UDI-6: Urogenital Distress Inventory

ǂ IIQ-7: Incontinence Impact Questionnaire

**ICIQ-SF: International Consultation on Incontinence Questionnaire Short form

**Subgroup analysis**

Appendix B, 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 = .686). 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 = .403), 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 reintervention 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 an 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 reintervention (33%) can contribute to dissatisfaction. The results on subjective and objective cure are comparable with other studies regarding PDMS-U. Kowalik *et al* included patients with complicated SUI with a poor expected outcome and reported an equal subjective cure rate of 50% at 6 months follow-up (8). 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 less 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 reinterventions (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 reinterventions, 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 easy 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 cutoff 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 postmarketing 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.

## CONCLUSIONS

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.

## CONFLICT OF INTERESTS

Jan-Paul W.R. Roovers reports grants and personal fees from Urogyn BV and Coloplast, grants from Tehpa, personal fees from Boston Scientific and Promedon. Claudia R. Kowalik reports grants and personal fees from Urogyn BV. Pieter Minnee reports personal fees from Urogyn BV. Fenne M. Casteleijn, Mija Blaganje, Stephen Jeffrey, Rosa Enklaar, Ikram El Bouyahyaoui and Sandra E. Zwolsman have nothing to declare.

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**APPENDIX A:** 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[γ]) | 64 ± 13 | 61 ± 10.6 | 64 ± 12 | 63 ± 14.4 | 77.4 ± 6.3 |
| No surgery prior to PDMS-U n(%) | 70 (64) | 11 (44) | 10 (27.8) | 37 (92.5) | 9 (100) |
| With surgery prior to 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 months n(%) | 21 (18) | 0 (0) | 17 (47) | 1 (4.2) | 0 (0) |
| 13-24 months n(%) | 29 (25) | 4 (16) | 19 (53) | 2 (8.3) | 0 (0) |
| >24 months n(%) | 51 (44) | 21 (84) | 0 (0) | 21 (87.5) | 2 (100) |
| **Site and physician characteristics** | | | | | |
| Type of hospital | | Academic hospital | General hospital | General hospital | Teaching hospital |
| Profession physician | | Gynecologist | Urologist | Urologist | Urologist |
| Total performed Urolastic procedures | | 67 | 67 | 57 | 23 |
| **Outcomes** | | | | | |

**APPENDIX A:** Overview outcomes *per site*

| | Overall | Site 1 | Site 2 | Site 3 | Site 4 |
|---|---|---|---|---|---|
| **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) |
| **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) |

**APPENDIX A:** Overview outco*mes per site*

| | Overall | Site 1 | Site 2 | Site 3 | Site 4 |
|---|---|---|---|---|---|
| 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) |
| **Complications and re-interventions n(%)** | | | | | |
| Urinary retention | 24 (21.8) | 1 (4) | 10 (27.7) | 8 (20) | 5 (56) |

**APPENDIX A:** Overview outco*mes per site*

| | Overall | Site 1 | Site 2 | Site 3 | Site 4 |
|---|---|---|---|---|---|
| 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) |
| Re-injection | 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 |

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

ˠ SD: Standard Deviation

ǂ IQR: Interquartile Range

*Surgical Satisfaction Questionnaire

†ICIQ**:** International Consultation on Incontinence Questionnaire Short Form

‡IIQ: Incontinence Impact Questionnaire Short Form

^UDI: Urogenital Distress Inventory Short Form

**APPENDIX B:** Subgroup analysis

| | 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)ᵞ | | 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 |
| BMI (median, IQR) | 26.9 (24.2-29.4) | | 26.5 (24.4-30.1) | | 27.2 (24.4-30.1) | |
| **BMI, categorical** (p)ᵞ | | 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)ᵞ | | 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 prior to PDMS-U vs. with surgery prior to PDMS-U**(p)ᵞ | | **0.04** | | 0.27 | | 0.44 |
| No surgery prior to PDMS-U (n,%)ǂ | 16(37.2) | | 20 (40.8) | | 23 (46.9) | |
| With surgery prior to PDMS-U (n,%)ǂ | 19 (61.3) | | 20 (52.6) | | 21 (55.3) | |
| **Subanalyses for procedural characteristics** | | | | | | |
| **Procedure 1-20 vs. >20** (p)ᵞ | | 0.42 | | 0.06 | | **<0.01** |

**APPENDIX B:** Subgr*oup analysis*

| | Objective cure | Subjective cure | Satisfied |
|---|---|---|---|
| 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)ʏ | **<0.01** | 0.19 | 0.66 |
| 1[i] (n,%)ǂ | 8 (32) | 7 (28) | 10 (40) |
| 2[2] (n,%)ǂ | 19 (79.2) | 20 (55.6) | 20 (55.6) |
| 3[3] (n,% )ǂ | 7 (30.4) | 12 (50) | 13 (54.2) |
| 4[4] (n,%)ǂ | 1 (50) | 1 (50) | 1 (50) |

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

[i] Site 1: Academic hospital

[2] Site 2: General hospital

[3] Site 3: General hospital

[4] Site 4: Teaching hospital

† Mann Whitney U

ʏ Chi-square

ǂ Percentages presented as within categorical group

^Continuous variable

# Chapter 01

# 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

### 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 (>150 mL) was the most common adverse event (40%), but persisted in only one patient, based on the patient’s preference for a catheter.

### Conclusions

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). Cure (dry) rates with these longer used biomaterials have been reported to range between 24% and 47% at 12 months for Polyacrylamide hydrogel (PAHG) and 36% for PDMS after

more than 18 months of follow up (7-9). 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 centres – like ours-preserve PBI for the most severe cases.

In recent history new treatment modalities have been introduced and also implemented within urogynaecology without thorough evaluation of safety and efficacy. We felt the need to properly evaluate this in situ polymerizing 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.

## METHODS

We performed a prospective observational study in two Dutch teaching hospitals with a special interest in urogynaecology. The medical ethics review committee of the Academic Medical Centre 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-h 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 that 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 500 mg orally as antibiotic prophylaxis 1h before the procedure, the other center performed the PBI without antibiotic prophylaxis.

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 (Figure 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 h women commenced with clean intermittent catheterisation (CIC) until a PVR of less than 150 mL was obtained.



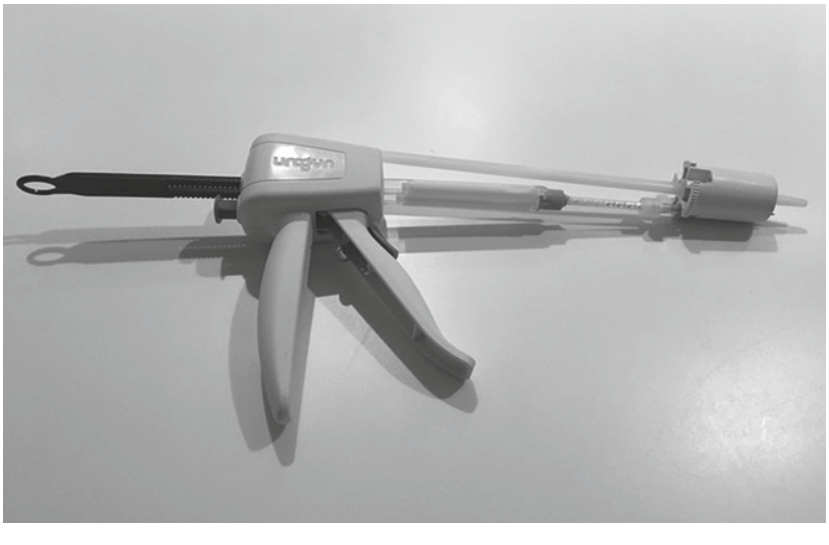

**Figure 1.** Urolastic device

**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 to 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 to 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 16 women (80%) completed follow up of 6 months (study visit and questionnaires).

**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

### 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).

**PGII**

At 6 months follow up 18/20 (90%) of women reported subjective improvement. Two women that 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 ($P = 0.04$).

**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-7ǂ *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

ǂ IIQ-7: Incontinence Impact Questionnaire

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

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



### 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 2-17 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 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% and 43% (15-17). 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 13-17% 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.

## CONFLICT OF INTERESTS

Jan-Paul W.R. Roovers, Claudia R. Kowalik, Fenne M. Casteleijn and Sandra E. Zwolsman reports grants from Urogyn BV, during the conduct of the study and grants from Urogyn BV outside the submitted work. Hugo van Eijndhoven reports grants from Urogyn BV and personal fees from Pelvision BV outside the submitted work.

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# Chapter 

# Cost-effectiveness of urethral bulking polydimethylsiloxane-Urolastic® compared with mid-urethral sling surgery for stress urinary incontinence: a two-arm cohort study

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## ABSTRACT

### Objective

To investigate the cost-effectiveness of urethral bulking polydimethylsiloxane-Urolastic® (PDMS-U) compared with mid-urethral sling (MUS) surgery for stress urinary incontinence (SUI) at 1-year follow-up.

### Design

Prospective, two-arm cohort study with 2-year follow-up.

### Setting

International multicentre.

### Population

Women with moderate to severe SUI.

### Main outcome measures

Primary outcome was subjective cure (Patient Global Impression of Improvement).

### Secondary outcomes

objective cure (negative cough stress test), Urogenital Distress Inventory (UDI-6), complications and re-interventions. Cost-effectiveness outcomes: total costs, quality-adjusted life year (QALY) using IIQ7-scores (Incontinence Impact Questionnaire) and EQ-5D-5L, incremental cost-effectiveness ratio (ICER) and monetary benefit (adjusted for baseline confounders).

### Results

In all, 131 PDMS-U and 153 MUS surgery patients were treated. Subjective cure rates for MUS surgery and PDMS-U were, respectively: 101/112 (90%) versus 40/87 (46%), adjusted odds ratio (aOR; for age, body mass index [BMI], severity, type of urinary incontinence and previous SUI procedure) was 4.9. Objective cure rates for MUS surgery and PDMS-U were respectively: 98/109 (90%) versus 58/92 (63%), aOR 5.4. Average total costs for PDMS-U and MUS surgery were €3567 and €6688. ICER for MUS surgery cost €15 598 per IIQ QALY and €37 408 per EQ-5D-5L QALY. With a willingness to pay (WTP) of €25 000, MUS has a 84% chance of being cost-effective using IIQ, whereas PDMS-U has a 99% chance of being cost-effective using EQ-5D-5L.

**Conclusion**

MUS surgery is more cost-effective in realising improved disease-specific quality of life (QoL), while PDMS-U is more cost-effective in realising improved generic QoL.

**Keywords:** cost-effectiveness; mid-urethral sling surgery; stress urinary incontinence; urethral bulking; willingness to pay.

## INTRODUCTION

Stress urinary incontinence (SUI) is the involuntary loss of urine on effort or physical exertion or on sneezing or coughing (1). SUI is the most prevalent type of urinary incontinence, affecting 29% of women (2). With a growing and ageing population and an expected increase of 47.5% for SUI surgery in 2050, SUI is heading for a major public health issue accompanied by a large economic burden (3). Total annual health costs for urinary symptoms for women in 2000 by the UK National Health Service (NHS) were reported as high as 233 million pounds, excluding personal costs of 178 million pounds (4). To lower costs, treatment should have a high success rate in both the short- and long-term, avoiding further hospitalisation.

International guidelines propose mid-urethral sling (MUS), autologous fascial sling, colposuspension and urethral bulking as surgical options for SUI. Mid-urethral sling-surgery (MUS surgery) is one of the interventions with the highest cure rates in the short- and medium term (64.1%–89.4%) and has acceptable safety profiles (5-7).

Urethral bulking aims for coaptation of the urethral lumen by injecting depots peri- or transurethrally. Treatment outcomes in the short-term are inferior to MUS surgery (8). In current practice, urethral bulking is suggested to be used in patients who are not suitable candidates for surgery or patients with recurrent SUI after primary surgery (9).

As healthcare costs continue to rise, outpatient treatment is attractive. Urethral bulking therapy does not require hospitalisation or general anaesthesia and therefore is hypothetically less costly, although re-injections for maintaining continence (reported as common as 5%–65%) do increase the costs (10). Over a 1-year time horizon, Kunkle *et al*. concluded urethral bulking was more cost-effective, as the incremental cost-effectiveness ratio (ICER) for MUS surgery was higher than the US $50 000 willingness to pay (WTP) (11). Cost analysis of surgical treatments for SUI in the long-term with a 10-year or life-long time horizon showed that retropubic MUS was the most cost-effective option (12).

Polydimethylsiloxane Urolastic® (PDMS-U) is non-absorbable urethral bulking that does not require multiple re-injections. Prospective cohort studies showed objective success rates of 59%–68% at 12-month follow-up (13,14). If cure rates of PDMS-U were

non-inferior to MUS surgery, it can be assumed that PDMS-U is a more cost-effective treatment option. The aim of our study was to evaluate the clinical outcome and cost-effectiveness of PDMS-U and MUS surgery over a 1-year time horizon.

## METHODS

We performed an international, multicentre, prospective, two-arm cohort study comparing MUS surgery and urethral bulking PDMS-U. We added monitored data from another single-arm prospective cohort study of PDMS-U with the same study protocol. Both studies had a 2-year follow-up. Here we present the cost-effectiveness analysis with a time horizon of 12 months. The study was approved by the ethical committees of the participating centres. Funding was received from a nonrestricted grant from Urogyn Bv (Nijmegen, the Netherlands) and a grant from ZonMW (the Netherlands), which included external peer review for scientific quality and priority assessment from a patient panel. Neither funding source was involved in the writing process.

### Patients and selection

Patients with moderate to severe SUI were selected from 10 teaching hospitals (specialised in pelvic floor problems), in the Netherlands, Slovenia, South Africa and Canada. Patients willing to undergo either MUS surgery or PDMS-U were offered an option-grid including risks and benefits of MUS surgery and PDMS-U to help shared decision making. After treatment decision, inclusion and exclusion criteria were met. Inclusion criteria were: female, ≥18 years with moderate or severe SUI or stress predominant mixed urinary incontinence (Sandvik severity scale ≥ 3) and a positive result on the standardised cough stress test (CST). Exclusion criteria were: predominating urge incontinence, genital prolapse with a POP-Q score of point Aa or Ba ≥0, pregnancy or intention to become pregnant during study, untreated urinary tract infection, bladder capacity of <250 ml, post-void residual volume of >150 ml, urinary flow of <15 ml/s, not capable of giving informed consent. Allocation of the intervention was led by patient preference.

### Procedures

PDMS-U was injected peri-urethrally and under local anaesthesia in an office setting. Antibiotic prophylaxis was not routinely used. Deposits of 0.8 mL were injected at the 10 o'clock and 2 o'clock positions, and 0.8–1.0 mL at the 5 o'clock and 7 o'clock positions. Possible excessive material was removed by forceps directly after the procedure. In case of persistent SUI symptoms, re-injection (0.8 ml at 3 o'clock and 9 o'clock) was performed at least 6 weeks after the initial procedure.

MUS surgery included retropubic-TVT (RP-TVT), transobturator-TVT (TOT/TVT-O) or single incision mini-sling (SIMS). The type of MUS surgery was selected at the surgeon's discretion. Depending on the anaesthesia and local protocols, MUS surgery was performed in a day-procedure or patients were admitted for one night. Post-procedural management of PDMS-U and MUS surgery included a post-void residual (PVR) measurement. An indwelling catheter was inserted for 24 h or clean intermittent self-catheterisation was applied in patients with either persistent PVR > 150 ml or initial PVR > 300 ml.

**Outcome measures**

***Clinical outcomes***

The primary outcome was subjective cure, defined as 'very much better' or 'much better' on the Patient Global Impression of Improvement (PGI-I) questionnaire. Secondary outcomes were: objective cure, defined as a negative CST (with a filled bladder of ≥250 ml in lithotomy or supine position), disease-specific Quality of Life (QoL) using short versions of the Incontinence Impact Questionnaire (IIQ-7) and Urogenital Distress Inventory (UDI-6), the Euro-QoL five-dimensional measure of generic QoL (EQ-5D-5L) questionnaire, complications and performed re-interventions. Questionnaires were collected at baseline (except for PGI-I), 4–6 weeks of follow-up, 6 months, 12 and 24 months of follow-up.



***Health economic outcomes***

The following health economic outcomes were used:

- Total costs.
- Quality-adjusted life year (QALY) based on QoL scores from both the IIQ and EQ-5D-5L, calculated as linear extrapolations of the QoL scores over the year of follow-up using measurements at baseline, 4–6 weeks, 6 months and 12 months. The QALY outcomes range between 0 and 1, where 0 implies deceased and 1 implies full health.
- ICER representing the average extra costs for one additional QALY, reported for IIQ and EQ-5D-5L separately.
- Cost-effectiveness plane to depict the results from bootstrapping, visualising uncertainty.
- Cost-Effectiveness Acceptability Curve (CEAC) to show the proportion of bootstrap samples in which a certain ICER (or lower) was found, thereby providing more information regarding the uncertainty around cost-effectiveness.

- Monetary benefit when adjusted for baseline confounders, which represents: the benefit or surplus of QALYs for a range of willingness-to-pay values, deducting the costs.

**Costs and resource use**

The costs evaluated include direct medical costs, out-of-pocket expenses and the indirect non-medical costs of productivity loss. Direct medical costs included therapeutic interventions, personnel, re-interventions, hospital admissions, adverse events and specialist consultations. The costs of the (re-)interventions were calculated as follows: device costs + surgical consumables + costs of operating facilities + anaesthesia + personnel. Personnel costs were dependent on procedural time (divided every 15 min). Production loss was calculated based on questionnaire data concerning absence from work. Resources used in both groups were obtained from case report forms and patient administered cost-questionnaires. The Dutch costing guideline was used to determine the relevant unit costs, supplemented if necessary, with unit costing data from previous economic evaluations. Costs were expressed in Euros in 2021.

**Analysis**

Pearson's Chi-square test was used for categorical data and nominal data and the Mann–Whitney U-test for continuous data. Logistic regression was used for adjusted odds ratio (aOR) (adjusted for age, body mass index [BMI], severity of SUI, type of UI and previous SUI procedure). For UDI-6 scores, adjusted mean differences were estimated by linear regression models. A (two-sided) p-value of <0.05 was considered statistically significant.

**Health economic analysis**

For cost-effectiveness, we analysed QALYs based on QoL score from either the IIQ or EQ-5D-5L questionnaires. We conducted two analyses, unadjusted and adjusted for confounders. For the first, the ICER was calculated by dividing the difference in mean total costs by the difference in mean QALY. We bootstrapped the costs and effects for 5000 samples with replacement to obtain the 95% confidence intervals (95% CI) of skewed costs and effects. Results were visualised in the cost-effectiveness plane. We used the bootstrap samples to construct a Cost-Effectiveness Acceptability Curve (CEAC) with varying ICER cut-offs following Fenwick *et al* (15).

For the adjusted analyses, we utilised the net benefit regression framework (16,17). We assumed that one QALY was 'worth' €25 000, €50 000, €75 000 or €100 000, multiplied this value by individual QALY scores to derive the monetary 'benefit', and then deducted their accumulated costs from their benefit. Next, we ran linear regression on the resulting net benefit adjusting for treatment group, age, BMI, baseline IIQ or

EQ-5D-5L, severity of incontinence (Sandvik severity scale) and type of incontinence (SUI or mixed urinary incontinence) and previous SUI procedure. We bootstrapped this analysis 5000 times per monetary value, then calculated the proportion of times in which MUS or PDMS-U yielded a higher net benefit. Data cleaning and descriptive data analysis were undertaken using SPSS version 28.0. Health economic analysis was undertaken in R version 3.6.0 (R Core Team, 2019) using the rms, foreign, mice, and dplyr R packages (18).

**Missing data**

When unit costs of MUS devices were missing, mean unit costs of the MUS type (RP-TVT, TVT-O/TOT or minisling) were used. When data on productivity loss were missing, the median number of lost working days per treatment group was used. If one or more QoL measures were missing, we extrapolated the QALY over the 12 months using those that were measured. Missing data on adverse events or re-interventions were neutralised and set at €0.

**Sensitivity analysis**

To assess the influence of calculating the QALY over the year of follow-up instead of merely the QoL score at the end of follow-up, we repeated the primary analysis with the IIQ and EQ-5D-5L scores at 12 months. A second sensitivity analysis aimed to assess the influence of missing data on productivity loss, in which these missing data were considered 'no productivity loss' (i.e. set at €0), was performed.

**Power analysis**

The power calculation was based on our primary outcome, subjective cure, with an expected efficacy for PDMS-U and MUS surgery of 72% (19) and 83% (6) respectively. With a significance level of 0.05 (one-sided), power of 80% and attrition rate of 10%, 240 patients (120 per group) were needed.

## RESULTS

From March 2017 to August 2020, 300 patients were included, of which 284 patients were treated, 131 with PDMS-U and 153 with MUS surgery. An inclusion and follow-up flow is available online (Appendix A). Table 1 lists the patients and treatment characteristics. In the PDMS-U group, patients were on average twice as old, had more severe SUI, more mixed urinary incontinence and a higher number of previous surgical treatments for SUI.

**Table 1.** Patient and treatment characteristics

| | Total n=284 | PDMS-U n=131 | MUS-surgery n=153 | p-value |
|---|---|---|---|---|
| **Patient characteristics** | | | | |
| Age mean SD | 57.2 (14.2) | 67.1 (12.8) | 47.8 (9.0) | p=<0.01 |
| BMI mean SD | 28.4 (18.5) | 30.7 (26.2) | 26.3 (4.6) | p=0.06 |
| Menopausal status | | | | p=<0.01 |
| Premenopausal n(%) | 98 (34.6) | 17 (12.9) | 81 (52.9) | |
| Perimenopausal n(%) | 23 (8.1) | 5 (3.8) | 18 (11.7) | |
| Postmenopausal n(%) | 135 (47.5) | 101 (77.1) | 34 (22.2) | |
| Unknown | 28 (9.8) | 8 (6.1) | 20 (13.1) | |
| Smoker | | | | p=0.14 |
| Yes n(%) | 32 (11.3) | 15 (11.5) | 17 (11.1) | |
| No n(%) | 211 (74.3) | 102 (77.8) | 109 (71.2) | |
| Unknown n(%) | 41 (14.4) | 14 (10.7) | 27 (17.6) | |
| Sandvik severity score | | | | p=<0.01 |
| Mild n(%) | 1 (0.3) | 1 (0.7) | 0 (0) | |
| Moderate n(%) | 64 (22.5) | 19 (14.5) | 45 (29.4) | |
| Severe n(%) | 199 (70.1) | 105 (80.2) | 94 (61.4) | |
| Unknown | 20 (7.1) | 6 (4.6) | 14 (9.2) | |
| Type urinary incontinence | | | | p=<0.01 |
| SUI n(%) | 189 (66.5) | 72 (54.9) | 117 (76.5) | |
| Stress dominated mixed urinary incontinence n(%) | 89 (31.3) | 57 (43.5) | 32 (20.9) | |
| Unknown | 6 (2.1) | 2 (1.5) | 4 (2.6) | |
| Previous operation for SUI | | | | p=<0.01 |
| Yes n(%)* | 59 (20.8) | 53 (40.4) | 5 (3.3) | |
| *Burch colposuspension* | *9 (3.2)* | *7 (5.3)* | *1 (0.6)* | |
| *RP-TVT* | *17 (5.9)* | *17 (12.9)* | *0* | |

**Table 1.** *(Continued)*

| | Total n=284 | PDMS-U n=131 | MUS-surgery n=153 | p-value |
|---|---|---|---|---|
| *TOT/TVT-O* | *30 (10.5)* | *27 (20.6)* | *3 (1.9)* | |
| *SIMS* | *3 (1.1)* | *2 (1.5)* | *1 (0.6)* | |
| *Urethral bulking* | *9 (3.2)* | *9 (6.8)* | *0* | |
| *Other* | *9 (3.2)* | *8 (6.1)* | *1 (0.6)* | |
| No n(%) | 224 (78.9 | 76 (58) | 148 (96.7) | |
| Unknown | 1 (0.3) | 2 (1.5) | 0 | |
| **Treatment characteristics** | | | | |
| Type MUS-surgery | | | | |
| RP-TVT | - | - | 15 (9.8) | |
| TOT/TVT-O | - | - | 66 (43.2) | |
| SIMS | - | - | 72 (47) | |
| Anesthesia | | | | |
| General | - | - | 48 (31.4) | |
| Spinal | - | - | 32 (20.9) | |
| Local analgesia with sedation | - | - | 71 (46.4) | |
| Volume PDMS-U depot (ml) | | | | |
| 10 o'clock | - | 0.86 | - | |
| 2 o'clock | - | 0.86 | - | |
| 5 o'clock | - | 1 | - | |
| 7 o'clock | - | 1 | - | |

BMI: Body Mass Index; MUS: mid-urethral sling; PDMS-U: polydimethylsiloxane-Urolastic; RP-TVT: retropubic tension free vaginal tape; SD: standard deviation; SIMS: single incision minisling; TOT/TVT-O: transobturator vaginal tape.

*some patients have had multiple previous operations for SUI, therefore numbers of specification of operation and "yes" does not match

### Clinical outcomes

Subjective and objective cure rates were lower in the PDMS-U group during all follow-up visits compared with MUS surgery. At 1-year follow-up, the subjective cure was 101/112 (90.1%) for MUS surgery and 40/87 (45.9%) for PDMS-U ($p \leq 0.01$). The aOR (adjusted for age, BMI, severity, type of urinary incontinence and previous SUI procedure) for subjective cure was 4.9 (95% CI 1.7–14.3). Objective cure was 98/109 (89.9%) for MUS surgery and 58/92 (63.0%) ($p \leq 0.01$) for PDMS-U; aOR was 5.4 (95% CI 1.8–15.9). Mean UDI-6 scores at baseline for PDMS-U and MUS surgery were respectively 49.8 and 46.8 ($p = 0.19$), giving an adjusted mean difference of 6.1 (95% CI for difference: 0.3–11.8). At 12-month follow-up, the scores were 32.7 for PDMS-U

and 16.7 for MUS surgery ($p \leq 0.01$), giving an adjusted mean difference of −19.6 (95% CI for difference: −28.0 to −11.2).

**Safety outcomes**

Table 2 shows the complications and re-interventions. Urinary retention and urinary tract infection were both common in the two treatment groups. Exposure of bulk material PDMS-U was prevalent in 23.6% and excision of PDMS-U in 19.8%. Higher numbers of surgical re-interventions were found in the PDMS-U group. Re-injection of PDMS-U was only performed in six patients.

**Total costs**

A total overview of resource use and costs is available online (Appendix B). Table 2 shows the costs of both treatment groups divided by categories. The average total costs of all categories were €3567 (95% CI 3168–4017) for PDMS-U and €6688 (95% CI 6129–7283) for MUS, with a mean difference of €3120 (95% CI 2382–3861). Re-intervention costs were higher for PDMS-U. Productivity loss costs were higher for MUS surgery.

**Table 2.** Safety outcomes and costs

| Complications | PDMS-U n=131 | MUS-surgery n=153 |
|---|---|---|
| Peroperative complications n(%) | 0 | 4 (2.6) |
| Bleeding | 0 | 1 |
| Vaginal wall perforation | 0 | 1 |
| Bladder perforation | 0 | 2 |
| Urinary retention n(%) | 28 (21.4) | 11 (7.2) |
| Days of catheterization (median) | 3 | 2 |
| UTI n(%) | 20 (15.3) | 27 (17.6) |
| Urgency de novo n(%) | 7 (5.3) | 5 (3.3) |
| Pain n(%) | 5 (3.8) | 3 (1.9) |
| Dyspareunia n(%) | 13 (9.9) | 2 (1.3) |
| Exposure through vaginal wall n(%) | 31 (23.6) | 1 (0.6) |
| 10 o'clock | 3 | - |
| 2 o'clock | 3 | - |
| 5 o'clock | 6 | - |
| 7 o'clock | 7 | - |
| Multiple locations | 6 | - |
| Unknown | 6 | - |
| Other n(%) | 10 (7.6) | 6 (3.9) |
| Hematoma | 3 | 2 |
| Late onset urinary retention | 1 | 4 |
| Erosion through urethra | 2 | 0 |
| Loss of bulking material | 3 | - |

**Table 2.** *(Continued)*

| **Complications** | | | **PDMS-U n=131** | | **MUS-surgery n=153** |
|---|---|---|---|---|---|
| Infection at injection site | | | 1 | | 0 |
| **Re-interventions** | | | **PDMS-U** | | **MUS-surgery** |
| Pelvic floor muscle training n(%) | | | 0 | | 7 (4.6) |
| Re-injection PDMS-U n(%) | | | 6 (4.6) | | - |
| Anti-incontinent surgery n(%) | | | 8 (6.1) | | 1 (0.7) |
| Burch colposuspension | | | 1 | | 0 |
| RT-TVT | | | 1 | | 1 |
| TOT/TVT-O | | | 2 | | 0 |
| Fascia sling | | | 1 | | 0 |
| Urethral bulking | | | 3 | | 0 |
| Excision PDMS-U / Sling n(%) | | | 26 (19.8) | | 1 (0.7) |
| **Medical costs** | **Data completion n/N (%)** | | **Costs mean (95% CI)** | | **Mean difference 95% CI** |
| | **PMDS-U** | **MUS-surgery** | **PDMS-U** | **MUS-surgery** | |
| Intervention | 131/131 (100) | 110/153 (72) ¥ | 1300 (1295 to 1305) | 930 (886 to 974) | -414 to -325 |
| Hospital admission | 130/131 (99) | 153/153 (100) | 0 (0 to 0) | 517 (489 to 545) | 491 to 547 |
| Adverse events | 104/131 (79) | 110/153 (72) | 58 (-3 to 107) | 8 (1 to 14) | -108 to -8 |
| Re-intervention | 111/131 (85) | 153/153 (80) | 265 (109 to 420) | 21 (7 to 34) | -418 to -112 |
| Additional visits | 131/131 (100) | 153/153 (100) | 26 (15 to 36) | 19 (7 to 32) | -22 tot 10 |
| **Non-medical costs** | | | | | |
| Productivity loss; paid work‡ | 121/131 (92) | 130/153 (85) | 1196 (796 to 1595) | 4767 (4128 to 5406) | 2834 to 4309 |
| Productivity loss; unpaid work‡ | 109/131 (83) | 138/153 (90) | 730 (580 to 881) | 426 (278 to 574) | 2158 to 3699 |

**Table 2.** *(Continued)*

| Complications | | | PDMS-U n=131 | | MUS-surgery n=153 |
|---|---|---|---|---|---|
| Productivity loss; paid work – sensitivity analysis | 121/131 (92) | 130/153 (85) | 975 (589 to 1362) | 3913 (3219 to 4606) | -509 to -98 |
| Productivity loss; unpaid work – sensitivity analysis | 109/131 (83) | 138/153 (90) | 582 (425 to 739) | 271 (138 to 404) | -511 to -109 |
| **Total costs** | | | 3567 (3168 to 4017) | 6688 (6129 to 7283) | 3120 (2382 to 3861) |

CI: confidence interval; MUS: mid-urethral sling surgery; PDMS-U: polydimethylsiloxane-Urolastic; RP-TVT: retropubic tension-free vaginal tape; TOT/TVT-O: transobturator vaginal tape; UTI: urinary tract infection

¥ in 43 patients, data on unit costs of MUS devices were missing (SIMS n=3, TVT-O/TOT n=32, R-TVT n=8)

‡missing data was imputed with median number of loss of working days per treatment group

### Quality-adjusted life year

Data was available for 284 women, 231 of whom had completed at least one IIQ or EQ-5D-5L during follow-up, allowing us to calculate QALYs. The median IIQ Quality of Life score at 12-month follow-up was 0.71 (interquartile range [IQR] 0.54–0.96) for PDMS-U and 1.00 (0.94–1.00) for MUS. The median IIQ QALY over the year of follow-up was 0.68 (IQR 0.50–0.81) for PDMS-U and 0.91 (0.79–0.98) for MUS, with a mean difference of 0.20 (0.15–0.25). The median EQ-5D-5L Quality of Life score at 12-month follow-up was 0.88 (0.82–1.00) for PDMS-U and 1.00 (1.00–1.00) for MUS. The median EQ-5D-5L QALY over the year of follow-up was 0.88 (IQR 0.82–0.96) for PDMS-U and 0.99 (0.92–1.00) for MUS, with a mean difference of 0.08 (0.05–0.12).

### ICER and cost-effectiveness plane

For IIQ, the ICER was €15 598 (95% CI 10 950–21 966), meaning that by spending €15 598 on MUS, one would gain one additional QALY as compared with PDMS-U. In Figure 1A, we visualised the bootstrap samples in the cost-effectiveness plane. All samples (100%) appeared in the north-east plane, meaning MUS is more expensive than PDMS-U, but also more effective. For EQ-5D-5L, the ICER was €37 408 (95% CI 22 817–67 102). Figure 1B shows that all samples (100%) appeared in the north-east plane; again, MUS is more expensive than PDMS-U, but also more effective.

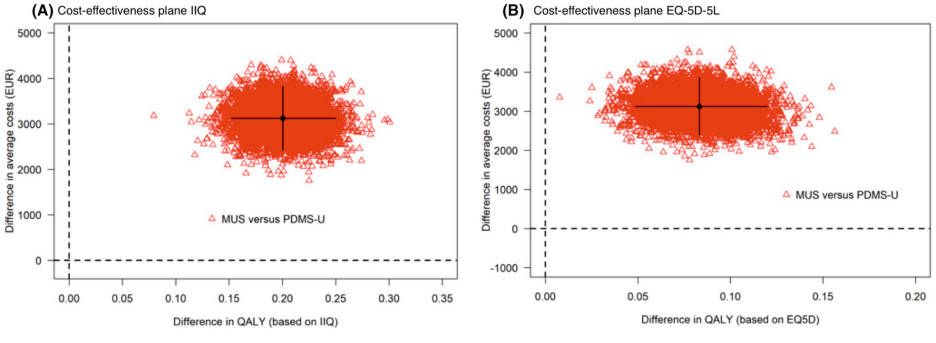


**Figure 1. This plane shows differences in costs and IIQ QALYs (A) and EQ5D5L QALY's (B) of bootstrap samples. All bootstrap samples are situated in the north-east plane, meaning mid-urethral sling surgery is more effective and more expensive compared to polydimethylsiloxane Urolastic®.**

### Cost-Effectiveness Acceptability Curve

Figure 2 provides more information on the uncertainty surrounding the cost-effectiveness. We found that at a WTP of €40 000 for one additional QALY, MUS has a 100%

chance of being cost-effective on the IIQ QALY scale, but a 59% chance of being cost-effective on the EQ-5D-5L QALY scale.

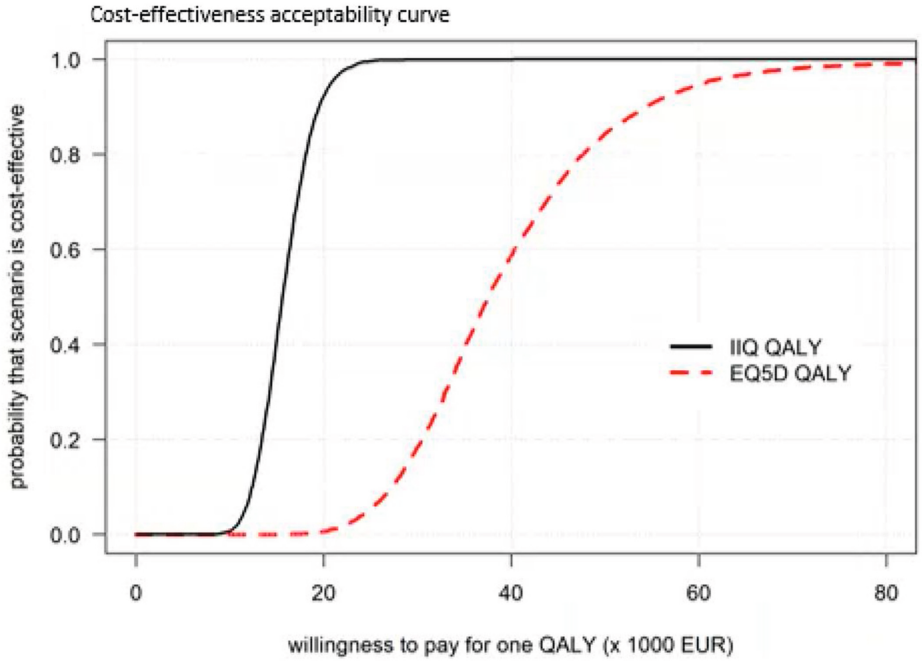


**Figure 2.** This curve shows the proportion of bootstrap samples (y-axis) that were found cost-effective when compared with a range of threshold monetary values (x-axis).

### Adjusted analysis

In the adjusted analyses, we found that in 84% of bootstrap samples, MUS yielded a higher net benefit than PDMS-U when one IIQ QALY was considered worth €25 000, increasing to 98% for €50 000 (or higher). In the adjusted analyses, we found that in 99% of bootstrap samples, PDMS-U yielded a higher net benefit than MUS when one EQ-5D-5L QALY was considered worth €25 000. Thus, this was the biggest difference between IIQ and EQ-5D-5L QALY scales. This decreased to 89% for €50 000, 69% for €75 000 and 55% for €100 000, meaning that with one EQ-5D-5L QALY considered worth €100 000, 45% of bootstrap samples showed that MUS yielded a higher net benefit than PDMS-U.

### Sensitivity analyses

In the sensitivity analyses including only women who (at least) completed the baseline and 12-month IIQ (n = 180) or 12-month EQ5D5L (n = 175), results for IIQ were identical to the primary analysis. For EQ-5D-5L, we found results that were more in favour of PDMS-U, as the average difference in QoL between groups was lower than the average difference in QALY. The ICER was now €47526 (95% CI 26400–134600).

In the sensitivity analysis, assuming zero leave days for women in which absenteeism data was missing, we found results that were slightly more in favour of MUS, as the average difference in costs was lower than in the primary analysis. The ICERs were €12365 (95% CI 7823–18283) for IIQ and €29889 (95% CI 16777–56204) for EQ-5D-5L.

## DISCUSSION

### Main findings

In this study we have shown that MUS surgery was more expensive and more effective than urethral bulking PDMS-U for treatment of SUI. The average extra costs for one additional QALY (ICER) for MUS surgery was €15598 per IIQ QALY and €37408 per EQ-5D-5L QALY. Adjusted analysis for baseline differences showed that with a WTP of €25000 for one disease-specific QoL (IIQ) QALY, MUS surgery had the highest probability to be cost-effective (in 84%), whereas for one generic QoL (EQ-5D-5L), PDMS-U had the highest probability to be cost-effective (in 99%).

### Strengths and limitations

We used both generic and disease-specific QoL outcome measures. Generic QoL outcomes can be more valuable for policy makers or for comparison across different diseases or interventions, whereas disease-specific QoL results can be more valuable for clinicians (20). We chose IIQ-7 and UDI-6 questionnaires for measuring disease-specific QoL because these questionnaires are incorporated in Dutch clinical practice and comprehensively assess symptom distress and the impact on daily life of urinary incontinence. Another strong point is that costs associated to complications and re-interventions were included, unlike some other economic analysis of SUI surgical procedures (21).

The first limitation of this study is that we found major differences in baseline characteristics between the two treatment groups. We chose a cohort-based study as, in-depth interviews showed that patients felt reluctant to be randomized (22). Moreover, physicians did not support conducting a trial, because at that point little was known

about the safety of PDMS-U. Although we put forward an option grid to stimulate shared decision making, selection bias did occur. In the adjusted analysis we corrected for confounders. Consequences of a cohort design is that patients are offered the treatment they prefer, impacting subjective outcomes positively (23). We hypothesise, however, that the effect size of this preference effect is equal for both treatment groups, and that in terms of bias, confounding is more likely. Secondly, the attrition, i.e. percentage of lost to follow-up, was 26%. We used mean value substitution and complete case analysis as missing data approaches, but these methods fail to cover the uncertainty in the data and may have introduced bias (24). We neutralised the missing data on adverse events and re-interventions, but it is expected that this has made little difference compared with all other costs. Data for a number of cost items were so often missing that we decided to remove these items from analysis: namely, pad use, postoperative painkillers and travel costs. As, from a patient's perspective, pad use is the biggest expense, this perspective should be considered underestimated, hypothetically at the expense of MUS surgery. Thirdly, some cost items were not included in the Dutch costing guideline and were extracted from the literature (Appendix A). Fourthly, there may be limitations in the generalisability of our results, as the majority of costs were based on Dutch costs, which may be very different from costing models in other regions. Lastly, the time horizon of 12 months may not have captured all relevant complications in the longer term. For example, mesh exposure was found in one patient in our study where the literature reports rates as high as 4.4% and 2.7%, for respectively TVT and TOT at 2-year follow-up (25).



**Interpretation**

The lower effectiveness of PDMS-U than MUS surgery is in line with a meta-analysis comparing surgical treatment with urethral bulk injection therapy (subjective improvement relative risk [RR = 0.70, 95% CI 0.53–0.92]) (26). The long-lasting, non-absorbable PDMS-U distinguishes itself from other bulking agents. In the light of cost-effectiveness, this seems relevant. Chang *et al.* allowed patients up to three injections at a 4-month interval and showed that over a time horizon of 2 years, urethral bulk injection therapy was more expensive (US $8789 vs. $5816) and thus MUS surgery more cost-effective (27). Oremus *et al.* also showed that surgery was more cost-effective than collagen if more than two re-injections were indicated (28,29). In our study, the re-injection rate of PDMS-U was low (4.6%), but the considerable exposure (23.6%) and excision rate (19.8%) resulted in higher re-intervention costs compared with MUS surgery. In this study the exposure rates were much higher than the 7.3% exposure rate of PDMS-U we found in our previous study of patient satisfaction (30). The most likely reason for this difference is that the exposure rates were under-reported in our previous study due to the cross-sectional study design.

With increasing total healthcare expenditure growth rates in the UK (from 3% to 6.2% between 2017 and 2019) and increasing pressures to control costs in healthcare, there is an ongoing ethical tension between cost-effectiveness and affordability for treatment decision making among policymakers (31). The National Institute for Health and Clinical Excellence (NICE) uses an ICER threshold between £20 000 and £30 000 per QALY (32). For clinicians and health insurers, our study supports that MUS surgery would be the preferred option compared with PDMS-U, as the disease-specific QoL (IIQ) of a WTP of €25 000 for MUS surgery is relatively low, acceptable to the NICE criteria and yielded greater net benefit in 84%. For the elderly it could be that improvement in generic QoL is found more relevant than disease-specific QoL and thus PDMS-U would be the preferred option.

Future prediction models dealing with patient characteristics could help assess individual value and costs ratios and allow personalised decisions.

## CONCLUSION

Mid-urethral sling surgery is more expensive and more effective than urethral bulking PDMS-U for treatment of SUI; ICER of €15 598 per IIQ QALY and €37 408 per EQ-5D-5L QALY. MUS surgery is more cost-effective in realising improved disease-specific QoL, whereas PDMS-U is more cost-effective in realising generic QoL. When adjusted for baseline differences, a WTP of €25 000 for one IIQ QALY had an 84% probability for MUS surgery to be cost-effective, whereas with outcome measure EQ-5D-5L, the WTP for MUS surgery would be over €100 000 to have a similar probability to be cost-effective.

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## CONFLICT OF INTERESTS

Le Mai Tu: Research Grant Fotona. John P.F.A. Heesakkers: Research Grant Medtronic. Consulting fees: BSCI, Kuste. Payments or honoraria for lectures, presentations: Astellas, Medtronic, Urogyn, BSCI. Payment for expert testimony: Dekra. Participating in DSMB: Kuste. Boards: ICS, EAU, NVU, AAEU. HE: Payments or honoraria for proctoring

Coloplast. Jan-Paul W.R. Roovers: Consulting fees: Coloplast, Promedon. Fenne M. Casteleijn, Rik van Eekelen, Allert M. de Vries, Yani Latul, Claudia R. Kowalik and Hugo W.F. van Eijndhoven declare no conflicts of interest.

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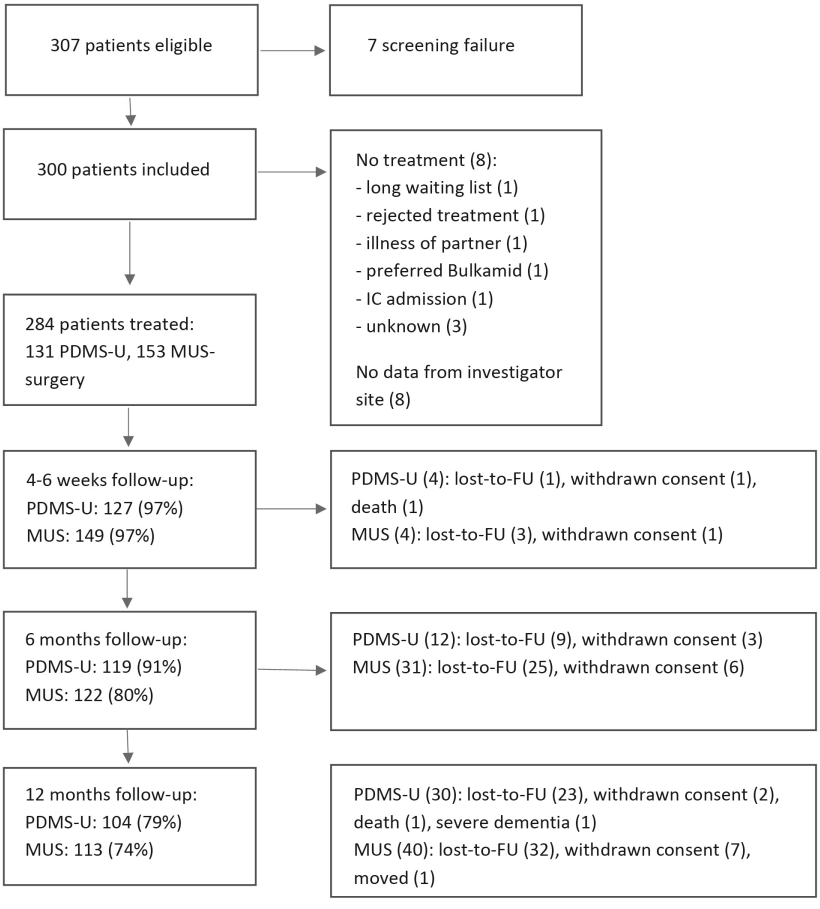
**APPENDIX A:** Inclusion and follow-up flow




Inclusions and follow-up of groups PDMS-U and MUS-surgery during the study.
PDMS-U: polydimethylsiloxane-Urolastic; MUS: mid-urethral sling; FU: follow-up; IC: intensive care

**APPENDIX B:** Cost overview

| | Cost item | Costs | Specification | Source |
|---|---|---|---|---|
| **Medical expenses** | | | | |
| Treatment device | PDMS-U | € 989,90 | Per unit | Extraction from hospital |
| | Solyx minisling | € 262,63 | Per unit | Extraction from hospital |
| | Ajust minisling | € 555,56 | Per unit | Extraction from hospital |
| | Altis | € 353,54 | Per unit | Extraction from hospital |
| | TVT-O | € 938,50 | Per unit | Extraction from hospital |
| | RP-TVT | € 353,54 | Per unit | Extraction from hospital |
| | Autologous fascial sling | € 6.565,65 | Per unit | Extraction from hospital |
| | Bulkamid bullking agent injection | € 914,00 | Per unit | |
| | Burch colposuspension | € 5.743,76 | Per unit | Lo -referentielijst |
| | Surgical consumables | € 51,55 | Cost per case | Valpas - referentielijst |
| Anesthesia | Local anesthesia | € 1,39 | Per case | Farmacotherapeutisch kompas |
| | Local anesthesia and sedation | € 24,94 | Propofol, Bupivacaine 0.5%, Lidocaine 1% | Farmacotherapeutisch kompas |
| | Spinal anesthesia | € 121,89 | total costs (minus personnel) | [y] |
| | General anesthesia | € 227,14 | total costs (minus personnel) | [y] |
| Personnel | Gynaecologist, urologist, anesthesiologist | € 88,22 | General hospital, cost per hour | Dutch costing guideline |
| | Nurse | € 34,33 | General hospital, cost per hour | Dutch costing guideline |
| Hospital admission | Nursing day | € 482,47 | General hospital, cost per day | Dutch costing guideline |
| Overhead costs | Operating facilities and capital costs | € 143,75 | Cost per case | Ankardal - referentielijst |
| Treatment adverse events | Nitrofurantoin 50mg | € 3,10 | Per urinary tract infection | Farmacotherapeutisch kompas |
| | Augmentin | € 3,71 | Per urinary tract infection | Farmacotherapeutisch kompas |
| | Betmiga 50mg | € 0,90 | Per day | Farmacotherapeutisch kompas |

**APPENDIX B:** C*ost overview*

| | Cost item | Costs | Specification | Source |
|---|---|---|---|---|
| | Vesicare 5mg | € 0,77 | Per day | Farmacotherapeutisch kompas |
| | Distigmine | € 1,35 | Per day | Farmacotherapeutisch kompas |
| | Toviaz | € 1,06 | Per day | Farmacotherapeutisch kompas |
| | Urodynamics | € 104,63 | Per item | referentielijst - Kobelt |
| | Botoxinjection bladder | € 3.538,81 | Per treatment | ‡ |
| | Indwelling catheter | € 2,10 | Per item | Medical shopping site |
| | Urinary bags | € 5,40 | Per item | Medical shopping site |
| **Consultation** | Pelvic floor physiotherapist | € 35,94 | Per vist | Dutch costing guideline |
| **Productivity loss** | Productivity costs | € 34,42 | Per hour, working female | iMTA costing tool |
| | Unpaid work | € 15,25 | Per hour, replacement costs | iMTA costing tool |

iMTA: Institute for Medical Technology Assessment; PDMS-U: polydimethylsiloxane; RP-TVT: retropubic TVT; TVT(-O): tension free vaginal tape (obturator)

ʏ reference: A. Chakladar, S. M. White; Cost estimates of spinal versus general anaesthesia for fractured neck of femur surgery

‡ ref: Real World Performance of Sacral Neuromodulation and OnabotulinumtoxinA for Overactive Bladder: Focus on Safety and Cost. Bilal Chughtai et al. J Urol. 2020 Jan;203(1):179-184.

# Chapter 4

# Sexual Function Following Treatment for Stress Urinary Incontinence With Bulk Injection Therapy and Mid-Urethral Sling Surgery

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## ABSTRACT

### Background

Peri-urethral bulking injections (PBI) gain popularity for the treatment of stress urinary incontinence (SUI), but – in contrast to mid-urethral sling (MUS) surgery – little is known about its impact on sexual function.

### Methods

This was a secondary analysis of a prospective cohort study that included patients with moderate to severe SUI undergoing either MUS surgery or PBI with polydimethylsiloxane Urolastic (PDMS-U). The validated Dutch and English version of the 'Pelvic Organ Prolapse and/or Urinary Incontinence Sexual Function Questionnaire – IUGA Revised' (PISQ-IR) was used to assess sexual function at baseline, at 6 and 12 months of follow-up. For between-group analysis, differences in baseline characteristics were corrected using multivariate analysis of covariance.

### Outcomes

The primary outcome was the PISQ-IR single summary score of sexually active (SA) women following both procedures, calculated by mean calculation. Secondary outcomes were the PISQ-IR subscale scores of SA and non-sexually active (NSA) women, the proportions of sexual activity and subjective improvement ('Patient Global Impression of Improvement' (PGI-I)).

### Results

A total of 259 women (MUS: n = 146, PBI: n = 113) were included in this study. The PISQ-IR single summary score of SA women improved following both interventions (in the MUS group from 3.2 to 3.4 and in the PBI group from 3.0 to 3.3 after 12 months). After correcting for differences in baseline characteristics, the PISQ-IR summary score at 6 and 12 months was similar for both treatment groups. For SA women, condition-specific and condition-impact subscale scores significantly improved following both procedures.

### Clinical implications

In treating SUI, PBI is inferior to MUS surgery. However, there is a need for less invasive strategies, especially for women who are unfit for surgery or have contraindications. Sexual function improves after PBI using PDMS-U, which is relevant for the counselling of women with SUI about available treatment options.

**Strengths & limitations**

Strength: until this study, there was a lack of knowledge about the effects of PBI on sexual function. Limitation: there may be indication bias as we did not perform a randomized controlled trial.

**Conclusion**

PBI using PMDS-U and MUS surgery for the treatment of SUI improve sexual function equally in SA women, mainly by decreasing the condition's impact on sexual activity and quality.

## INTRODUCTION

Stress urinary incontinence (SUI) is a common condition in women of all ages with prevalence rates up to 35% (1-3). Besides the negative impact on women›s social, physical and psychological wellbeing, SUI negatively influences sexual function and wellbeing in up to 68% of affected women (4). Physically, frequent urinary leakage irritates the vulvovaginal region which can lead to dyspareunia. On emotional level, SUI negatively affects self-esteem, sexual desire and sexual satisfaction (4). Up to 45% of women with urinary incontinence completely avoids sexual activity because of their symptoms (5,6). SUI seems to affect the sexual function of patients' partners as well (7,8).

Multiple studies demonstrate that treating SUI – either conservatively or surgically – improves sexual well-being, function and self-esteem (9-14). Surgical interventions are highly effective at controlling urinary incontinence and thereby improve the overall quality of life (15). Therefore, it is reasonable to presume that surgical interventions improve sexual function. However, treatment-specific complications may impair sexual function. Following mid-urethral sling (MUS) surgery, sling exposure and neurovascular tissue damage may cause sensory loss, pelvic pain, dyspareunia (16-19). Accordingly, studies do not consistently report improvement of sexual function following surgical interventions for SUI (20,21). Some studies demonstrate no effect on, or even deterioration of sexual function and *de novo* dyspareunia is reported even in studies that demonstrate improved sexual function after surgery (12,22-25).

An alternative, minimally invasive surgical intervention to treat SUI comprises peri-urethral bulking injections (PBI). PBI involves the injection of material around the urethra intending to increase urethral coaptation and thereby restoring urinary continence (26). PBI can be performed under local analgesia in an ambulatory setting and enables fast return to daily activities. Compared to invasive surgical approaches, PBI has a lower cure rate, but a more favourable safety profile (26,27). Therefore, it should be presented as a treatment option to women who have contraindications for MUS

surgery or recurrent SUI. PBI is associated with minor tissue damage and even though complications (such as retention, pain at the injection site, haematuria and infection) do occur, they are mild and transient. Therefore, these complications may cause less sexual impairment than the complications associated with MUS surgery. Polydimethylsiloxane Urolastic (PDMS-U) is a nonbiodegradable bulking agent that polymerises after injection, resulting in encapsulated deposits with a low risk of migration. As PDMS-U is non-absorbable and non-deformable, long-term treatment effects are expected (28). In patients that are not optimal candidates for MUS surgery, PBI using PDMS-U results in good subjective and objective cure outcomes (29). The effect of PBI using PDMS-U on sexual function has not been evaluated yet. Moreover, there is a lack of knowledge about the effects on sexual function of PBI in general. In the present study, we evaluated and compared the impact of MUS surgery and PBI using PDMS-U on sexual function over a follow-up period of 1 year.

## METHODS

Data for this study was obtained from a multicentre, prospective cohort study on efficacy, safety and cost-effectiveness of peri-urethral bulking agent polydimethylsiloxane Urolastic (PDMS-U) injections versus MUS surgery in women with SUI. We added monitored data from another single-arm prospective cohort study of PDMS-U with the same study protocol. The trial was registered in the Dutch Trial Register (Identifier NTR7590) (30). The study was reviewed and approved by the ethical committee of the Amsterdam UMC and the boards of all participating centres. All participants received verbal and written explanation of the study procedures and provided informed consent. The current study on sexual function includes data obtained from 13 institutes worldwide (see Appendix A).

### Study Design

The validated Pelvic Organ Prolapse and/or Urinary Incontinence Sexual Function Questionnaire – IUGA Revised (PISQ- IR) was used to assess sexual function at baseline and after 6 and 12 months of FU (31). The primary outcome was the PISQ-IR single summary score of sexually active (SA) women (32). The primary objective was to evaluate the impact of both MUS surgery and PBI using PDMS-U on the PISQ-IR single summary score and to compare the PISQ-IR single summary scores between treatment groups after 12 months of FU. The secondary objectives were to evaluate the impact of both procedures on (i) the PISQ-IR subscale scores of SA and non-sexually active (NSA) women, (ii) the proportions of sexual activity, and (iii) subjective improvement.

**Population**

Women with moderate to severe SUI or stress predominant mixed urinary incontinence (Sandvik severity scale ≥ 3) were eligible for participation if they were at least 18 years old, had a positive cough stress test and had opted for treatment with either MUS surgery or PBI by shared decision making (33). Exclusion criteria were: predominant urge incontinence, pelvic organ prolapse with POP-Q of point Aa or Ba ≥ 0, pregnancy, untreated urinary tract infection, bladder capacity <250mL, post-voiding residue of >150mL and flow <15mL/sec.

**Interventions and Study Procedures**

*MUS Procedures*

Surgical (MUS) procedures were performed following established institutional protocols and national standards of care. Under general anaesthesia, spinal analgesia or sedation, a retropubic-, transobturator- or single incision mid-urethral sling was placed.

*Peri-Urethral Bulking Injections*

The bulking agent used in this study was Urolastic (Urogyn BV, Nijmegen, the Netherlands), which is a CE-certified product that consists of PDMS-U. Procedures were performed under local analgesia by certified physicians who had followed specific training to perform this procedure. The exact procedures of this bulking agent have been described before (28,34). In short, the bulking agent is injected into the submucosal tissue around the mid-urethra at 10, 2, 5 and 7 o'clock positions. Several seconds after injection, the deposits solidify, creating artificial cushions compressing the mid-urethra and thereby improving urethral coaptation.

*Assessment of Sexual Function*

The validated Dutch and English versions of the PISQ- IR were used to assess sexual function (31). The PISQ-IR is a disease-specific questionnaire that was developed based on the PISQ-12, to assess sexual function in both SA and NSA with pelvic floor dysfunction. As SUI causes avoidance of sexual activity in many affected women, treating SUI might change the proportions of sexual activity and inactivity, which makes the evaluation of sexually inactive women relevant. The provided answers result in ten subscale scores. The subscales for NSA women are NSA-CS (condition-specific reasons for not being active), NSA-PR (partner-related reasons for not being active), NSA-GQ (global quality rating of sexual quality) and NSA-CI (condition impact on sexual quality). Higher NSA subscales indicate a greater impact of the condition on sexual function. For SA women, subscales are SA-AO (assessment of arousal, orgasm), SA-PR (assessment of partner-related impacts), SA-CS (assessment of condition-specific

impacts on activity), SA-GQ (global quality rating of sexual quality), SA-CI (condition-specific impact on sexual quality) and SA-D (assessment of sexual desire). In the subscales for SA women, higher scores indicate better sexual function. PISQ-IR questionnaires were completed at baseline and after 6 months and 12 months of FU.

***Assessment of Subjective Improvement of SUI Symptoms***

Subjective improvement of SUI symptoms following both procedures was evaluated after 6 and 12 months of FU by the 1 item questionnaire 'Patient Global Impression of Improvement' (PGI-I), which includes a 7-point Likert scale ranging from "1 = very much better" to "7 = very much worse" (35).

**Statistical Analysis**

As recommended by the authors of the original publication, the PISQ-IR results were analysed separately for SA and NSA women (36). The summary score was calculated by mean calculation according to instructions published by Constantine *et al.* (2017) (32). To calculate the summary score, a minimum of provided responses is required (11 of 21 specific question items for SA women with a partner and 9 of 18 for SA women without a partner) (32). If insufficient items were responded to, the questionnaire was excluded from the evaluation of summary scores. The different subscale scores were scored by mean calculation using the scoring program provided by IUGA (available at https://www.iuga.org/resources/pisq-ir). Means and standard deviations (SD) are reported for normally distributed continuous variables, medians (μ) and interquartile ranges (IQR) for non-normally distributed continuous variables and absolute and relative frequencies for categorical variables. For the between-group comparative analysis of continuous and categorical variables, an independent t-test, Mann-Whitney U or Pearson Chi-Square test was used. For between-group analysis of PISQ-IR single summary scores, differences in baseline characteristics were corrected using multivariate analysis of covariance (MANCOVA) (37). Comparative analysis within groups over time was performed using a Wilcoxon signed ranks test for non-normally distributed continuous data and the McNemar test for categorical data. A 2 sided P value below 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics (IBM Corp. Released 2020. IBM SPSS Statistics for Macintosh, Version 27.0. Armonk, NY: IBM Corp).

## RESULTS

A total of 259 women were enrolled in this study, of which 146 (56%) underwent MUS surgery and 113 (44%) underwent the PBI using PDMS-U. Of these women, 236 (91%) completed the PISQ-IR questionnaire at baseline, 168 (65%) after 6 months of FU and 174 (67%) after 12 months of FU. PGI-I was completed by 195 participants (75%) after 6 months and 175 participants (77%) after 12 months of FU. For the evaluation of PISQ-IR summary scores, respectively 1, 20 and 9 completed questionnaires had to be excluded at baseline, 6 and 12 months of FU because of an insufficient number of provided responses.

The clinical characteristics of the participating women are presented in Table 1. Women who underwent PBI were significantly older than women who underwent MUS surgery (69 (21) vs 48 (11) years old, $P < 0.01$). In the PBI treated group, more women were postmenopausal (67.9% vs 26.4%, $P < 0.01$), more were using vaginal oestrogen therapy (11.5% vs 2.9%, $P < 0.01$) and more had undergone prior surgical interventions for pelvic organ prolapse or UI (40.7% vs 10.3%, $P < 0.02$) than the MUS treated group. Of the women who underwent PBI, fewer had a partner (53.9% vs 77.4%, $P < 0.01$), and fewer were sexually active at baseline (51.0% vs 80.3%, $P < 0.01$) than women who underwent MUS surgery (Table 1).

Women who reported to be sexually active at baseline were younger (49 (12) vs 68 (21) years old, $P < 0.01$) and more frequently had a partner (81.2% vs 44.8%, $P < 0.01$) than women who considered themselves not sexually active. The proportion of sexually active women did not change over time following both procedures (MUS: 80% (baseline) vs 85% (6 months) vs 82% (12 months), PDMS-U: 51% (baseline) vs 54% (6 months) vs 54% (12 months)).

Women reported subjective improvement (PGI-I) of SUI symptoms following both procedures, which was greater following MUS surgery (“very much better”) than PBI (“a little better”, Table 1).

**Table 1. Patients characteristics**

| | MUS (N = 146) | PDMS-U (N = 113) | *P* value | SA (N = 159) | NSA (N = 77) | *P* value |
|---|---|---|---|---|---|---|
| Patient characteristics | | | | | | |
| Age at inclusion in years, μ (IQR)[a] | 48 (11) | 69 (21) | <0.01 | 49 (12) | 68 (21) | <0.01 |
| Vaginal deliveries, μ (IQR)[a] | 2 (1) | 2 (1) | 0.73 | 2 (1) | 2 (1) | 0.40 |
| BMI, μ (IQR)[a] | 25.8 (5.8) | 27.2 (6.4) | 0.12 | 25.6 (5.5) | 28 (5.7) | <0.01 |
| Postmenopausal patients, %[b] | 26.4% | 67.9% | <0.01 | 35.9% | 74.3% | <0.01 |
| Prior surgical intervention for POP or UI*, %[b] | 10.3% | 40.7% | <0.01 | 20.8% | 31.2% | 0.08 |
| Vaginal oestrogen therapy, %[b] | 2.9% | 11.5% | <0.01 | 6.1% | 9.1% | 0.44 |
| Prolapse grade II or higher, %[b] | 22.6% | 27.9% | 0.43 | 23.4% | 21.2% | 0.76 |
| Has a partner, %[b] | 77.4% | 53.9% | <0.01 | 81.2% | 44.8% | <0.01 |
| Questionnaire outcomes | | | | | | |
| Sexually active baseline, %[b] | 80.3% | 51.0% | <0.01 | 100% | 0% | |
| PGI-I 6 months**, μ (IQR)[a] | 1 (1) | 3 (1) | <0.01 | 2 (2) | 2 (2) | 0.23 |
| PGI-I 12 months**, μ (IQR)[a] | 1 (1) | 3 (2) | <0.01 | 1 (2) | 2(2) | <0.01 |

a = Mann-Whitney U, b = Pearson Chi-Square

⁎ Includes anterior and/or posterior vaginal wall repair with and without Mesh, colposuspension (sacrocolpopexy, sacrospinal fixation, Manchester operation, Burch colposuspension), TVT (retropubic sling), TVT-O/TOT (transobturator sling), SIMS, bulking agent.

† PGI-I responses are: 1 = “very much better”, 2 = “much better”, 3 = “a little better”, 4 = “no change”, 5 = “a little worse”, 6 = “much worse” and 7 = “very much worse”).

‡ Mann-Whitney U.

§ Pearson Chi-Square.

BMI = body mass index; IQR = interquartile range; MUS = mid-urethral sling; N = number of patients; NSA = non-sexually active; PDMS-U = bulking agent polydimethylsiloxane Urolastic; POP = pelvic organ prolapse; PGI=I = patient global impression of improvement; SA = sexually active; UI = urinary incontinence; **μ = median.** Comparison between treatment groups (MUS and PDMS-U) and between SA and NSA. Bold P values indicate statistical significance (ie, P < 0.05).

**Table 2.** PISQ-IR scores of SA women

| | Baseline | | 6 months | | | 12 months | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean ± SD | N | Mean ± SD | *P* value * | N | Mean ± SD | *P* value * |
| **Single summary score** | | | | | | | | |
| MUS | 106 | 3.2 ± 0.5 | 68 | 3.4 ± 0.3 | **<0.01** | 72 | 3.4 ± 0.3 | **<0.01** |
| PDMS-U | 52 | 3.0 ± 0.6 | 26 | 3.3 ± 0.4 | 0.47 | 32 | 3.3 ± 0.4 | **<0.05** |
| **Subdomains** | | | | | | | | |
| *SA-AO* | | | | | | | | |
| MUS | 104 | 3.7 ± 0.8 | 94 | 3.9 ± 0.6 | 0.09 | 86 | 3.9 ± 0.5 | **<0.01** |
| PDMS-U | 52 | 3.4 ± 0.7 | 30 | 3.4 ± 0.7 | **<0.05** | 35 | 3.3 ± 0.7 | 0.12 |
| *SA-CS* | | | | | | | | |
| MUS | 100 | 3.8 ± 1.0 | 88 | 4.5 ± 0.6 | **<0.01** | 81 | 4.6 ± 0.6 | **<0.01** |
| PDMS-U | 45 | 3.7 ± 0.9 | 27 | 4.1 ± 0.8 | **<0.05** | 33 | 4.3 ± 0.8 | **<0.01** |
| *SA-PR* | | | | | | | | |
| MUS | 101 | 3.6 ± 0.6 | 72 | 3.6 ± 0.7 | 0.63 | 80 | 3.6 ± 0.6 | 0.87 |
| PDMS-U | 46 | 3.5 ± 0.5 | 25 | 3.5 ± 0.5 | 0.32 | 30 | 3.5 ± 0.5 | 0.13 |
| *SA-D* | | | | | | | | |
| MUS | 104 | 3.1 ± 0.7 | 80 | 3.2 ± 0.7 | 0.82 | 83 | 3.2 ± 0.6 | 0.26 |
| PDMS-U | 53 | 2.9 ± 0.9 | 26 | 3.0 ± 0.7 | 0.98 | 33 | 2.8 ± 0.6 | 0.48 |
| *SA-CI* | | | | | | | | |
| MUS | 105 | 3.2 ± 0.8 | 80 | 3.7 ± 0.5 | **<0.01** | 83 | 3.8 ± 0.6 | **<0.01** |
| PDMS-U | 51 | 2.9 ± 0.9 | 27 | 3.4 ± 0.8 | **<0.05** | 33 | 3.3 ± 0.7 | **<0.01** |
| *SA-GQ* | | | | | | | | |
| MUS | 105 | 2.7 ± 0.6 | 79 | 2.5 ± 0.6 | **<0.01** | 82 | 2.4 ± 0.6 | **<0.01** |
| PDMS-U | 49 | 2.8 ± 0.9 | 26 | 2.9 ± 0.9 | 0.65 | 34 | 3.1 ± 0.8 | 0.17 |

* Wilcoxon signed ranks test.

AO = Arousal and orgasm; CS = Condition-specific; CI = Condition impact; D = Desire; GQ = Global quality; MUS = mid-urethral sling; N = number of included questionnaires; PDMS-U = polydimethylsiloxane Urolastic; PR = Partner related; SD = standard deviation; SA = sexually active. Mean PISQ-IR single summary and subscale scores of sexually active women at baseline, 6 and 12 months of follow up. Means and SDs are rounded to 1 decimal. *P* values compare follow up moment (6 or 12 months) to baseline. Bold *P* values indicate statistical significance (ie, $P < 0.05$).

**PISQ-IR Single Summary and Subscale Scores**

Single summary and subscale scores of SA women are presented in Table 2. Both procedures resulted in an increased single summary score 12 months after treatment. At 6 months of FU, this improvement was only significant for MUS and not for PDMS-U procedures. After correcting for differences in baseline characteristics, the PISQ-IR summary score was similar for both treatment groups at 6 months (MUS: 3.3 (95% CI [3.25-3.41]) vs PBI: 3.4 (95% CI [3.2-3.58])) and 12 months of FU (MUS: 3.4 (95% CI [3.35-3.51]) vs PBI: 3.5 (95% CI [3.29-3.60])). Condition-specific (SA-CS) and condition-impact (SA-CI) subscale scores significantly improved after 6 and 12 months of FU following both procedures, which indicates less impact of the condition on sexual activity (less urinary leakage and consequently less fear and shame during sexual activity) and less impact of the condition on sexual quality. The global quality subscale score did not change following PDMS-U procedures and even deteriorated following MUS surgery (Table 2). The arousal and orgasm subscale score was significantly higher at 6 months of FU for the PDMS-U treated group and at 12 months of FU for the MUS treated group. For NSA women, none of the subscale scores significantly changed following either procedure.

## DISCUSSION

The results of this study demonstrate that sexual function improves equally following bulk injection therapy with PMDS-U and MUS surgery in sexually active women with SUI after 6 and 12 months of follow-up, mainly by decreasing the condition's impact on sexual activity and quality.

Many studies have evaluated the impact of MUS surgery on sexual function before (11-14). A meta-analysis combining results of 23 studies demonstrated that the majority (67%) of women that underwent MUS surgery experienced unchanged or improved sexual function (17). Recently, Freitas *et al.* (2021) were the first to evaluate sexual function following PBI using polyacrylamide hydrogel injection (PAHG) in a randomized controlled trial using the PISQ-12 (38). They demonstrated that overall sexual function improved equally following TVT and PBI 1 year after procedures (38). They observed a particular improvement of the physical subscale, which was greater for TVT than PAHG. We observed improved physical subscales (condition-specific and condition impact) following both MUS and PDMS-U as well. After correction for differences in baseline characteristics, we demonstrated that sexual function was similar following both procedures. However, the reported subjective improvement (PGI-I) following both procedures differed substantially: improvement was significantly greater in the MUS treated group. Thus, even though PBI was less effective in treating SUI than MUS

surgery, improvement of sexual function was similar, indicating that factors different from symptom-relief affect sexual function.

One such factor might be sexual quality; for example, are sexual experiences enjoyable, satisfactory and pleasurable? Following MUS surgery, we observed a worsening of the global quality subscale score of SA women. Multiple studies have described *de novo* dyspareunia as a contributing factor for decreased sexual global quality following MUS surgery (12,39). Vaginal surgery can cause neurovascular tissue damage which may result in dyspareunia or sensory loss and thereby impair sexual function (19,40). Szell *et al.* (2017) demonstrated that despite overall improved sexual function following MUS surgery, only 33% of treated women experience improved orgasm function (17). Besides dyspareunia and decreased sensibility, patients with SUI report on multiple other factors that contribute to sexual satisfaction, including loss of self-esteem and psychological distress.[4] These psychological, rather than functional factors, might underly the impaired global quality observed in the women undergoing MUS surgery.

For sexually inactive women, none of the subscale scores significantly improved following either procedure. Women who were not sexually active before treatment remained sexually inactive after treatment. Multiple other studies describe no or little increase in sexual activity following treatment for SUI as well (11,38). Up to 45% of women with urinary incontinence completely avoid sexual activity because of their symptoms (5,6). In our population, resolving or relieving SUI symptoms did not result in improved function or increased activity. Therefore, it seems that the presence of SUI itself might not determine sexual inactivity. Other factors – such as sexual interest and partner status – might play a more prominent role. Within our study population, only 45% of NSA women had a partner, compared to 81% of SA women.

This study presents unique data on the impact of PBI on sexual function. We have used a validated disease-specific questionnaire (PISQ-IR) to assess the sexual function of women undergoing treatment for SUI (36). In contrast to other disease-specific questionnaires on sexual function, the PISQ-IR also encompasses both sexually active and inactive women. Thereby, we have provided insight into the impact of treating SUI on sexual activity and function in sexually inactive women with SUI, which gives a more comprehensive presentation of the sexual function of all women.

Some limitations of our research need to be addressed. First, we should be careful when comparing the outcomes of the MUS surgery group to the PDMS-U group because treatment allocation was not randomized, so we cannot correct for all potential confounders. In the study performed by Freitas *et al.* (2021), randomized treatment allocation resulted in similar baseline characteristics between both treatment groups (38). Because of the outspoken treatment preferences of physicians and patients, treatment allocation in our present study was not randomized. As a consequence,

patient characteristics were substantially different at baseline: women who underwent PDMS-U were much older, had undergone more prior surgical interventions, less frequently had a partner and were considerably less sexually active. As fewer women within this group were sexually active compared to the MUS treated group, fewer of their questionnaires could be included for evaluation of the summary score and SA-subscale scores. To enable comparison between treatment groups, we have corrected for these differences using MANCOVA. Second, we did not perform subgroup analysis with regards to the type of sling (eg, TOT, TVT, mini-sling), which might influence orgasm scores (17). Third, we studied the impact of 1 single bulking agent that might not reflect the impact of all other bulking agents. When translating our findings to other bulking agents, their specific characteristics such a biodegradability, absorbability and deformability should be taken into account.

Our present study demonstrates that overall sexual function improves equally following PBI using PDMS-U and MUS surgery. MUS surgery remains the more efficacious option for the treatment of SUI. PBI should be presented as a treatment option for SUI to women who have contraindications for MUS surgery or recurrent SUI. Sexually active women undergoing PBI using PDMS-U can expect an improvement in their sexual function. These findings will benefit the counselling of women with SUI about available treatment options. In order to implement PBI in common practice, efficacy and safety need to be studied more extensively.

## CONFLICT OF INTERESTS

Jan-Paul W.P. Roovers reports consultant of Coloplast. Yani P. Latul, Fenne M. Casteleijn and Sandra E. Zwolsman have nothing to declare.

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## APPENDIX A: Participating centers

Bergman Clinics Vrouw, Amsterdam, The Netherlands. Sint Antonius Ziekenhuis, Nieuwegein, The Netherlands. Radboud UMC, Nijmegen, The Netherlands. Spaarne Gasthuis, Haarlem, The Netherlands. Isala Klinieken, Zwolle, The Netherlands. Gelre Ziekenhuis, Apeldoorn, The Netherlands. Martini Ziekenhuis, Groningen, The Netherlands. Maxima Medisch Centrum, Eindhoven, The Netherlands. NoordWest Ziekenhuisgroep, Den Helder, The Netherlands. Slotervaart Ziekenhuis, Amsterdam, The Netherlands. Slingeland Ziekenhuis, Doetinchem, The Netherlands. Pretoria Steve Biko Hospital, Pretoria, South Africa. UMC Ljubljana, Ljubljana, Slovenia

## APPENDIX B: Supplementary Table 1: PISQ-IR scores of NSA women

### Supplementary Table 1: PISQ-IR scores of NSA women

| | Baseline | | 6 months | | | 12 months | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean ± SD | N | Mean ± SD | *P* value * | N | Mean ± SD | *P* value * |
| **Subdomains** | | | | | | | | |
| *NSA – PR* | | | | | | | | |
| MUS | 22 | 2.4 ± 1.1 | 13 | 3.0 ± 1.1 | 0.92 | 17 | 2.9 ± 0.9 | 0.52 |
| PDMS-U | 41 | 3.0 ± 1.0 | 22 | 3.1 ± 1.1 | 0.48 | 23 | 3.5 ± 0.8 | 0.19 |
| *NSA - CS* | | | | | | | | |
| MUS | 17 | 2.1 ± 0.9 | 8 | 2.4 ± 1.4 | 0.16 | 14 | 2.0 ± 1.3 | 0.55 |
| PDMS-U | 32 | 2.2 ± 1.1 | 16 | 2.2 ± 1.0 | 0.34 | 17 | 2.5 ± 1.1 | 0.83 |
| *NSA – GQ* | | | | | | | | |
| MUS | 21 | 2.1 ± 0.6 | 15 | 2.3 ± 0.8 | 0.54 | 15 | 2.4 ± 0.8 | 0.75 |
| PDMS-U | 43 | 2.1 ± 0.7 | 17 | 2.3 ± 0.6 | 0.37 | 18 | 2.3 ± 0.7 | 0.37 |
| *NSA – CI* | | | | | | | | |
| MUS | 21 | 2.2 ± 1.0 | 13 | 1.5 ± 0.9 | 0.24 | 14 | 1.5 ± 0.8 | 0.09 |
| PDMS-U | 42 | 2.2 ± 1.1 | 16 | 2.0 ± 0.8 | 0.51 | 19 | 2.3 ± 1.2 | 0.86 |

* Wilcoxon signed ranks test

Mean PISQ-IR subscale scores of sexually inactive women at baseline, 6 and 12 months of follow up. NSA = non-sexually active, PR = Partner related, CS = Condition-specific, GQ = Global quality, CI = Condition impact, MUS = mid-urethral sling, PDMS-U = polydimethylsiloxane Urolastic, N = number of included questionnaires, SD = standard deviation. Means and SDs are rounded to one decimal. *P* values compare follow up moment (6 or 12 months) to baseline.

# Chapter 8

# A clinical learning curve study of polydimethylsiloxane Urolastic for stress urinary incontinence: does safety improve when expertise grow?

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## ABSTRACT

### Objectives

To characterize the learning curve of bulk injection therapy PDMS-U for SUI.

### Design

Secondary analysis from three clinical studies on efficacy and safety outcomes of PDMS-U.

### Methods

PDMS-U certified physicians who performed ≥4 procedures were included. The primary outcome was the number of PDMS-U procedures needed to achieve acceptable failure rates for 'complications overall', 'urinary retention' and 'excision', using the LC-CUSUM method. For the primary outcome, physicians who performed ≥ 20 procedures were used. For the secondary outcome, logistic and linear regression analysis was used to assess the relationship between number of procedures, complications (complications overall, urinary retention, pain, exposure, excision of PDSM-U) and duration of treatment.

### Results

In total, 203 PDMS-U procedures were performed by nine physicians. Five physicians were used for the primary outcome. For 'complications overall', 'urinary retention' and 'excision', two physicians reached a level of competence: one at procedure 20 and one at procedure 40. The secondary outcome showed no statistically significant association between procedure number and complications. There was a statistically significant increase in the duration of treatment with more physician experience (mean difference 0.83 minutes per 10 additional procedures, 95%CI 0.16 to 1.48).

### Limitations

One limitation is that retrospectively collected data might have underreported the number of complications. Secondly, there was variation in the way the technique was applied between physicians.

### Conclusions

Physicians' experience in the PDMS-U procedure did not influence safety outcomes. There was large inter-physician variability and most physicians did not reach acceptable failure rates. There was no relationship between PDMS-U complications and the number of performed procedures.

## INTRODUCTION

Stress urinary incontinence (SUI) is a condition of involuntary loss of urine on effort, physical exertion, sneezing or coughing, and this condition affects around 29-40% of adult women (1-2). Urethral bulk injection therapy is receiving more attention as an alternative treatment option for SUI since safety issues for polypropylene mesh have emerged (3-5). Currently, bulk injection therapy is mainly used for patients who are poor candidates for surgery, patients with persistent or recurrent SUI after previous surgery and patients with intrinsic sphincter deficiency (6). A recent study showed high satisfaction scores following bulk injection therapy, although non-inferiority compared to mid-urethral sling (MUS) was not reached (7).

Polydimethylsiloxane Urolastic® (PDMS-U) is the most recently developed bulking agent and has non-deformable and non-absorbable properties. Theoretically, these characteristics result in more durable cure rates as compared to the more hydrophilic bulking agents that tend to be absorbed over time. Single surgeon prospective cohort studies showed objective cure rates following PDMS-U varying from 33% up to 67% (8). Overall complications of PDMS-U occurred in 24% of patients and included urinary retention, pain, haematuria, infection, urinary issues (frequency, urgency, incontinence) and erosion of the urethra/vaginal wall [9]. Excision rates were higher compared to other bulking agents, which seemed to be the consequence of the solidity of the material (9).

Physicians who start using PDMS-U need to complete a training program where they must perform at least three consecutive procedures under supervision of a PDMS-U specialist. Since the learning curve has never been investigated, it is not known whether this number of supervised procedures is sufficient. Assessment of learning curves is relevant because it provides insight into when a safe and competent level is reached, which can be useful for personalized training programs and quality control (10). In general, standard learning curves can be divided into three phases: initial difficulty with higher rates of errors or fails, improvement of outcomes and stabilization of performance (plateau phase) (11). As opposed to standard learning curves, cumulative summation for the learning curve (LC-CUSUM) takes acceptable and unacceptable failure rates into account to indicate performance. Competence is achieved when an acceptable failure rate is met (12).

The primary goal of this study was to characterize the learning curve of the PDMS-U procedure using the LC-CUSUM method per physician. Second, we aimed to determine whether overall safety outcomes were related to the number of performed procedures. We hypothesized that a low procedure number (which means a low level of experience) was related to a high probability of complications and a longer duration

of the procedure, whereas a high procedure number was related to a low probability of complications and a shorter duration of the procedure.

## METHODS

This study was a reanalysis of data from a cross-sectional study (approval number NL62993.018.17) (13), a prospective pilot study (W13_248#13.17.0343) (14) and an ongoing multicenter prospective cohort study (NL59107.018.16). These studies were reviewed and approved by the ethical committee of the Amsterdam UMC and the boards of all participating centres. Written informed consent for the use of safety data was obtained for participation in these studies. Reanalysis of anonymized data is covered by the previous approval of the three previously performed studies.

### Population

The inclusion criteria was: physicians were certified PDMS-U specialists that completed training. The exclusion criteria was: physicians who had performed less than four procedures.

### Training

The training program of PDMS-U, as designed by the manufacturer, consisted of a written physician training manual and supervision of at least three PDMS-U procedures. If trainees did not reach the required level of competence after three supervised procedures, extended supervision was possible. However, the required level of competence was not defined by objective measures.

### Intervention

Polydimethylsiloxane Urolastic® (Urogyn BV, Nijmegen, The Netherlands) was used in every patient. Patients were positioned in the lithotomy position. Local anaesthesia was used prior to injection. The urethral length was measured and the right applicator size was used to make sure the depots were injected at mid-urethral level. Para-urethral injections of 0.8cc-1.0cc PMDS-U were performed through the vaginal wall at 2 o'clock, 5 o'clock, 7 o'clock and 10 o'clock around the urethra. The place and depth of the injection were dependent on the length of the urethra and the size of the applicator. Thirty seconds after every injection, the needle was retracted. Three minutes after injection the substance was solidified and if necessary, excessive material leaking from the injection sites was removed using tweezers.

**Data collection**

The following complications within one year after PDMS-U were assessed: urinary retention (for which an indwelling catheter, intermittent catheterization or excision was indicated), hematoma, urinary tract infection (UTI) (within 6 weeks after treatment), urgency de novo, pain at the injection site, dyspareunia, exposure, erosion and excision of PDMS-U. Duration of the procedure (in minutes) was defined as the time between positioning the patients in lithotomy position and removing the excess of material after injection.

**Primary outcome – learning curve per physician**

For primary analysis physicians who performed ≥ 20 procedures were used. The primary outcome was the number of PDMS-U procedures needed for physicians to achieve a level of competence with regards to the occurrence of all abovementioned complications, using the LC-CUSUM method (12, 15). In LC-CUSUM, the physician is considered incompetent if unacceptable failure rates are met (H1) and is considered competent if acceptable failure rates are met (H0). Complication rates are plotted in LC-CUSUM graphs in Excel to show when a level of competence was reached. If the line crossed below boundary H0, competence was reached. If the line crossed the upper boundary H1, an unacceptable failure rate was reached. If the line stayed between H0 and H1, neither an acceptable nor unacceptable failure rate was reached. The acceptable failure rate was based on complication rates in literature and set at 24% (9). The unacceptable failure rate (H1) was set at 48% (doubling of acceptable failure rate) (16). Additionally, we specifically evaluated 'urinary retention' and 'excision' as separate complication outcomes. For urinary retention and excision, acceptable and unacceptable failure rates were respectively set at 10-20% and 11-22% (9). A post-hoc analysis excluding patients with surgical treatment for SUI prior to PDMS-U treatment for learning curves was performed (17).

**Secondary outcomes – probability of complications related to procedure number**

The secondary outcome of this study was to evaluate if complications and duration of treatment were related to the procedure number. All procedures that were performed (independent of the physician) were identified by their procedure number. We used logistic and linear regression analysis using the following complications: complications overall, urinary retention, pain, exposure, excision of PDSM-U and duration of treatment. Two subgroup analysis were performed, to determine if 1. the physicians experience with bulk injection therapy prior to PDMS-U and 2. hospital setting (teaching versus general) influenced safety outcomes ('complications overall' and 'excision').

### Statistical analysis

Descriptive statistics were provided for physicians' and patients' characteristics. We used Excel for the LC-CUSUM method to create graphs for each outcome in which per physician success and failure of each patient was plotted. A success (positive outcome) was plotted as decrease with decrement as calculated per outcome. A failure (negative outcome) was plotted as increase with increment as calculated per outcome. Missing data were not imputed (18). The values used to calculate the LC-CUSUM can be found in Appendix A.

For analysis of the secondary outcome, we used logistic regression for the binary outcomes and linear regression for the continuous outcome. As we expected the learning curve to be non-linear, we first looked at quartiles of procedure numbers in the regression models. If these associations were linear stepwise, we instead simplified by using procedure number as a continuous variable in the regression model, otherwise we kept the quartiles. For subgroup analysis, the Chi square test was used. Statistical analysis was performed using IBM SPSS Statistics 24 and Microsoft Excel 2016. A p-value of $<0.05$ was considered statistically significant.

## RESULTS

### Physicians and Patients

An overview of the physicians' characteristics is shown in Table 1a. Data from nine physicians (five urologists and four (uro)gynaecologists) were collected who performed a total of 203 PDMS-U procedures. The procedure numbers ranged from 1-66. Five out of nine physicians (56%) had previous experience with bulk injection therapy. Five physicians performed ≥ 20 procedures and were used for primary outcome analysis. An overview of the patients' characteristics is shown in Table 1b. The mean age of the included patients was 63.8 (±13.3) years and the mean BMI was 27.7 (±6.8). 71 (35%) patients had undergone MUS-surgery prior to the PDMS-U treatment. 10 (4.9%) had undergone Burch colposuspension and 10 (4.9%) had undergone bulk injection therapy other than PDMS-U prior to PDMS-U treatment. Re-injection was performed in 21 (10.3%) patients. Perioperative complications were observed in six patients and consisted of: excision because of too superficial location (sub-epithelial) of the bulking material (n=3), pain (n=2), hematoma (n=1). Device malfunction was observed once.

**Table 1a.** Physician characteristics

| Physician no | Type hospital | Type physician | Years of practice | Experience with BA | Specification (estimated no) | Included PDMS-U procedures | Range procedure no (median) |
|---|---|---|---|---|---|---|---|
| 1 | Teaching | Gynecologist | 9 | Yes | Bulkamid (120) | 33 | 1-66 (41) |
| | | | | | Opsys (61) | | |
| | | | | | Urodex (3) | | |
| | | | | | Autologous myoblasts (76) | | |
| 2 | Teaching | Urologist | 30 | Yes | Bulkamid (120) | 36 | 1-66 (33) |
| 3 | General | Urologist | 19 | Yes | Macroplastique (75) | 40 | 2-59 (34) |
| | | | | | Coaptite (75) | | |
| 4 | Teaching | Urologist | 19 | No | NA | 15 | 2-23 (12) |
| 5 | Teaching | Gynecologist | 7 | No | NA | 36 | 1-44 (18) |
| 6 | Teaching | Urologist | 20 | Yes | Bulkamid (10) | 6 | 1-6 (3) |
| 7 | Teaching | Gynecologist | 17 | No | NA | 23 | 1-23 (12) |
| 8 | Teaching | Urologist | 22 | Yes | Collagen (70) | 10 | 7-19 (12) |
| | | | | | Macroplastique (70) | | |
| | | | | | Zuidex (60) | | |
| 9 | Teaching | Gynecologist | 14 | No | NA | 4 | 1-4 (2) |

No: Number; BA: bulking agent; NA: not applicable; PDMS-U: polydimethylsiloxane Urolastic

**Table 1b. Patient characteristics**

| | n=203 | % |
|---|---|---|
| Age mean (SD) | 63.8 (13.3) | |
| BMI mean (SD) | 27.8 (6.8) | |
| Parity median (IQR) | 2 (2;3) | |
| Smoker | 26 | 12.8 |
| Urgency urinary incontinence | 88 | 43.3 |
| Pelvic organ prolapse POPQ stage ≥2 | 11 | 5.4 |
| Postmenopausal status | 158 | 77.8 |
| Sexually active | 103 | 50.7 |
| Hypermobile urethra | 40 | 19.7 |
| MUS-surgery prior to PDMS-U | 71 | 35 |
| Burch colposuspension prior to PDMS-U | 10 | 4.9 |
| Bulk injection therapy prior to PDMS-U | 10 | 4.9 |
| Other pelvic surgery | 31 | 15.4 |
| Anterior colporrhaphy | 6 | |
| Posterior colporrhaphy | 3 | |
| Myoblasts injection | 1 | |
| Hysterectomy | 15 | |
| Side specific repair | 1 | |
| Wertheim | 4 | |
| Adnexextirpation | 6 | |

BMI: Body Mass Index; POPQ: Pelvic Organ Prolapse Quantification; MUS-surgery: mid-urethral sling surgery; PDMS-U: polydimethylsiloxane Urolastic; no: number; SD: standard deviation; IQR: inter quartile range

**Primary outcome – Learning curve**

The LC-CUSUM graphs of the 5 physicians who performed a minimum of 20 procedures is shown in Figures 1a-c.

***Complications overall***

With regards to complications overall, only physician 4 achieved the level of competence, at procedure number 20 (Fig. 1a). All other physicians reached the unacceptable level of failure rate (H1).

***Urinary retention***

With regards to urinary retention, physician 1 reached the level of competence (H0) at procedure number 40 (Fig. 1b). Physicians 3 and 4 stayed between H0 and H1, whereas physicians 2 and 5 reached unacceptable failure rates (Fig. 1b).

***Excision***

With regards to excision of PDMS-U, none of the physicians achieved the level of competence. Physician 5 reached an unacceptable failure rate, and physicians 1-4 stayed between H0 and H1 (Fig. 1c).

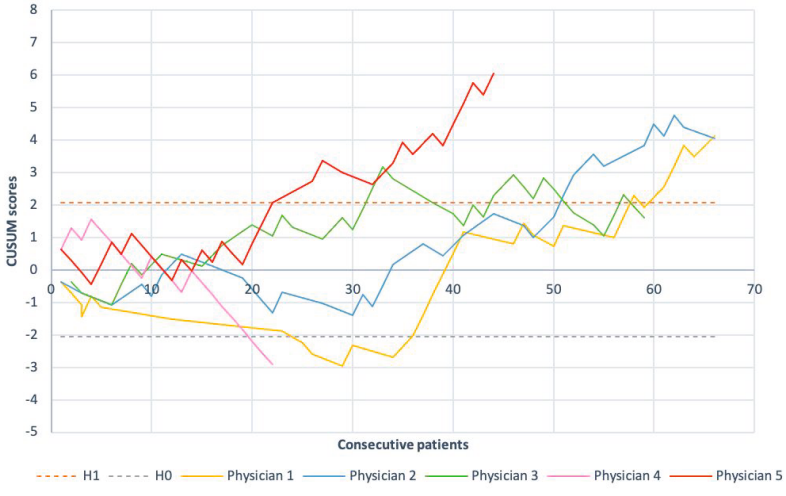


**Figure 1a: LC CUSUM graph of overall complications for 5 individual physicians.**
H0 = acceptable failure rate H1 = unacceptable failure rate



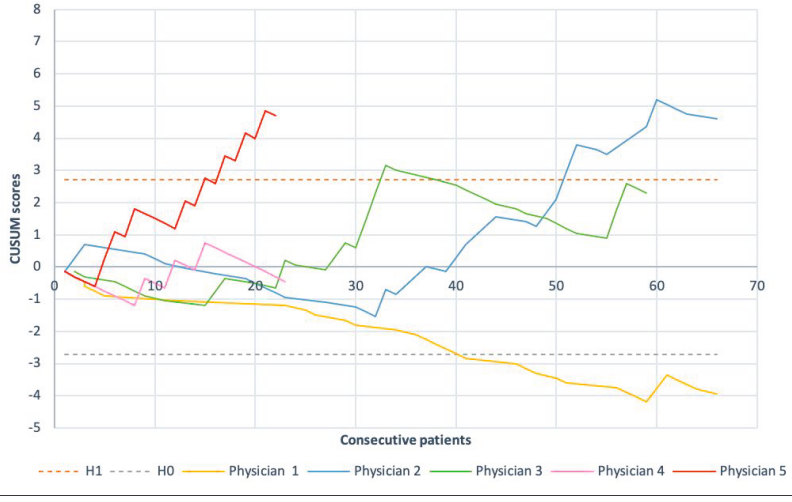


**Figure 1b: LC CUSUM graphs of retention for 5 individual physicians**
H0 = acceptable failure rate H1 = unacceptable failure rate

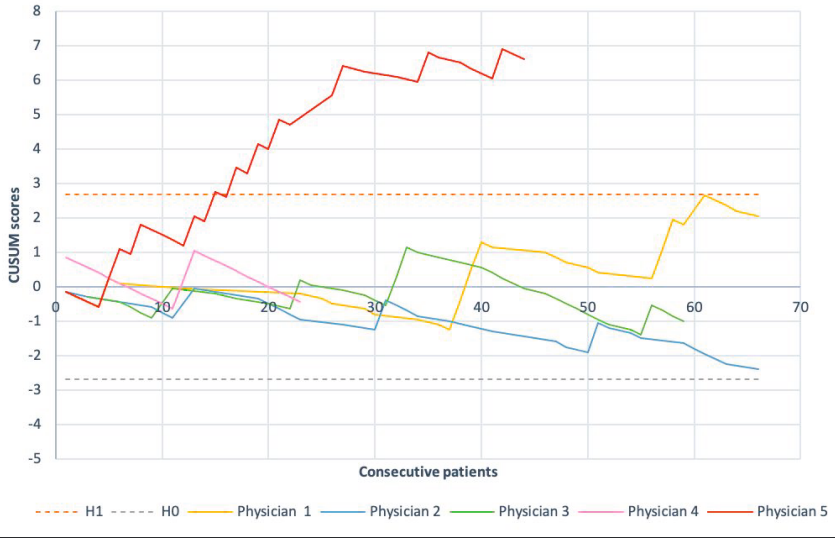


**Figure 1c: LC CUSUM graphs of excision for 5 individual physicians**
H0 = acceptable failure rate H1 = unacceptable failure rate

### Post-hoc analysis

Post-hoc analysis, in which patients with previous surgical treatment prior to PDMS-U treatment were excluded, is shown in Figures 2a-c. Except for physician 3, too little data remained to objectify a learning curve. With regards to physician 3, no major differences were found and the level of competence was not achieved.

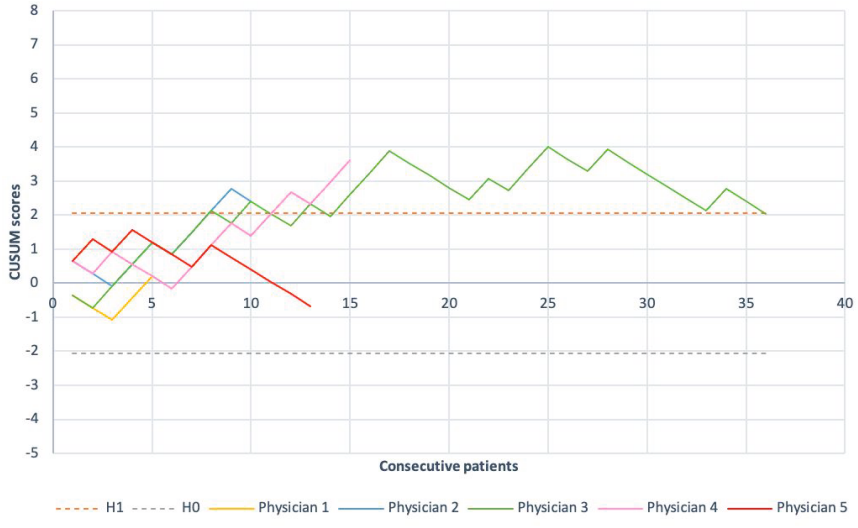


**Figure 2a: posthoc LC CUSUM graphs of overall complications of 5 individual physicians**
H0 = acceptable failure rate H1 = unacceptable failure rate

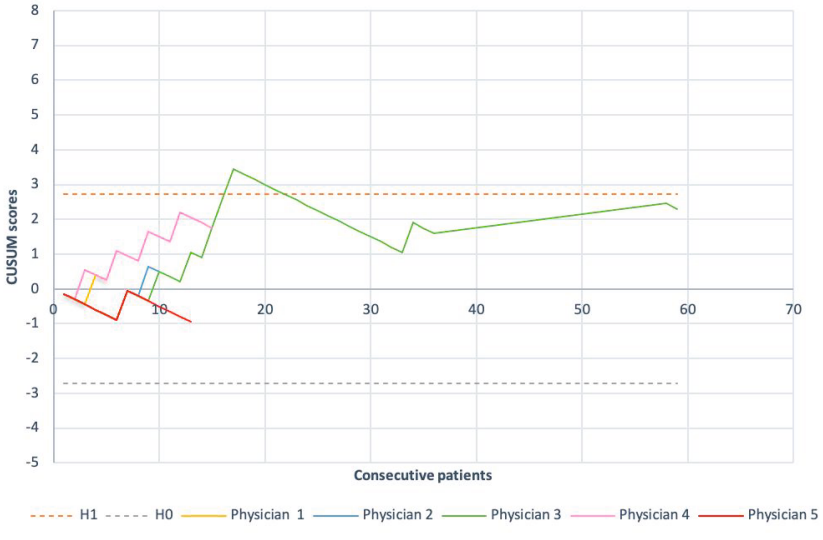


**Figure 2b: posthoc LC CUSUM graphs of retention for 5 individual physicians**
H0 = acceptable failure rate H1 = unacceptable failure rate

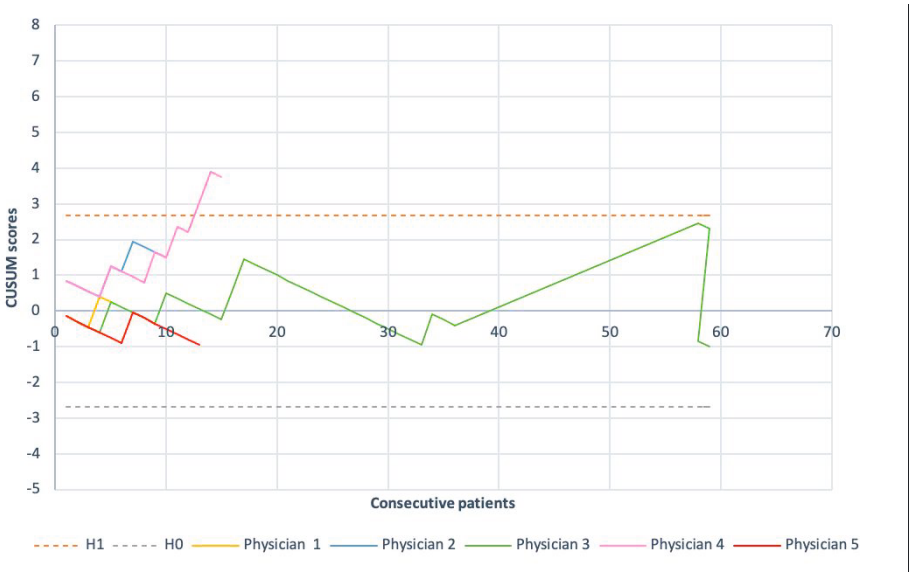


**Figure 2c: posthoc LC CUSUM graphs of excision for 5 individual physicians**
H0 = acceptable failure rate H1 = unacceptable failure rate

### Secondary outcomes – Complications related to procedure number

Prevalence of postoperative complications and duration of treatment related to procedure number are shown in Table 2. Urinary retention (occurrence 23.2%), excision (20.2%) and exposure of PDMS-U (14.3%) were the most common complications. None of the associations between procedure number and complications were statistically significant. There was a linear association between procedure number and urinary retention (odds ratio 0.997; 95% CI 0.83 to 1.19). The median duration of procedures was 21.9 ± 5.7 minutes. There was a small but significant linear association between procedure number and duration of the procedure (mean difference 0.826 minutes per 10 additional procedures, 95% CI 0.16 to 1.48).

Subgroup analysis of physicians' previous experience in bulk injection therapy prior to PDMS-U showed no significant difference on 'overall complications' (63/125 (50.4%) versus 39/78 (50%), p-value: 0.95) or 'excision' (22/123 (17.8%) versus 19/78 (24.3%), p-value: 0.09). Subgroup analysis of hospital setting (teaching hospital versus general hospital) showed no significant difference on 'overall complications' (86/163 (52.7%) versus 16/40 (40%), p-value: 0.14) or 'excision' (36/162 (22.2%) versus 5/39 (12.8%), p-value: 0.32).

**Table 2. Complications related to procedure number**

| | Procedure numbers | | | | | | | | Logistic or linear‡ regression | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total (n=203) | 0-10 (n=55) | 11-20 (n=45) | 21-30 (n=25) | 31-40 (n=26) | 41-50 (n=24) | 51-60 (n=19) | 61-70 (n=9) | OR or mean difference‡ | 95%CI | P-value |
| Complications overall n (%) | 102 (50.2) | 26 (47.3) | 24 (53.3) | 9 (36.0) | 16 (61.5) | 12 (50) | 10 (62.6) | 5 (55.6) | 1.045* (second quantile) | 0.50 to 2.33 | 0.58 |
| | | | | | | | | | 1.166* (third quantile) | 0.54 to 2.52 | |
| | | | | | | | | | 1.127* (fourth quantile) | 0.51 to 2.48 | |
| Urinary retention n (%) | 47 (23.2) | 10 (18.2) | 14 (31.1) | 6 (24) | 6 (23.1) | 4 (16.7) | 6 (31.6) | 1 (11.1) | 0.997† (OR per 10 procedures) | 0.83 to 1.19 | 0.97 |
| Pain n (%) | 27 (13.3) | 8 (14.5) | 5 (11.1) | 2 (8.0) | 2 (7.7) | 5 (20.8) | 2 (10.5) | 3 (33.3) | 0.598* (second quantile) | 0.18 to 1.97 | 0.44 |
| | | | | | | | | | 0.717* (third quantile) | 0.23 to 2.24 | |
| | | | | | | | | | 1.195* (fourth quantile) | 0.41 to 3.50 | |
| Exposure n (%) | 28 (14.3) | 9 (16.4) | 9 (20.0) | 2 (8.0) | 7 (26.9) | 1 (4.2) | 0 (0) | 1 (11.1) | 1.077* (second quantile) | 0.39 to 2.99 | 0.08 |
| | | | | | | | | | 1.228* (third quantile) | 0.45 to 3.34 | |
| | | | | | | | | | 0.111* (fourth quantile) | 0.01 to 0.92 | |
| Excision PDMS-U n (%) | 41 (20.2) | 11 (20.4) | 12 (26.7) | 2 (8.0) | 10 (38.5) | 1 (4.2) | 4 (21.1) | 1 (12.5) | 1.147* (second quantile) | 0.45 to 2.90 | 0.39 |
| | | | | | | | | | 1.275* (third quantile) | 0.51 to 3.19 | |
| | | | | | | | | | 0.455* (fourth quantile) | 0.14 to 1.42 | |
| Time of procedure mean (SD) | 21.9 (5.7) | 21.6 (6.1) | 19.5 (5.7) | 22.1 (6.4) | 23.4(4.7) | 25.2 (5.4) | 24.6 (1.1) | 25.3(0.6) | 0.826†‡ (mean difference per 10 procedures) | 0.16 to 1.48 | 0.01 |

PDMS-U: polydimethylsiloxane-Urolastic; SD: standard deviation

*non-linear associations found using quartiles as steps. The first quartile is the reference category.

† linear associations in the model

‡ fitted using linear regression

## DISCUSSION

Physicians' experience in PDMS-U did not influence safety outcomes. We found a large inter-physician variability and most physicians did not reach acceptable failure rates. Procedural time increased instead of decreased with more experience, albeit with a small amount that may be the result of noise.

The LC-CUSUM graphs showed wide distribution among the physicians and only two physicians reached level of competence. One factor that influences the learning curve is the physician's experience and exposure frequency. Subgroup analysis showed however that the physician's experience with bulk injection therapy prior to PDMS-U did not affect safety outcomes. The time period in which physicians performed the PDMS-U interventions varied considerably between physicians. For example, one physician performed all 23 procedures within two years, whereas another physician took over four years to perform 36 procedures. For the effective establishing of a learning curve and for a level of competence to be reached, execution of the intervention is ideally frequent after the introduction to the new procedure.

A second factor that could contribute to the wide distribution in LC CUSUM graphs is the heterogeneity of patients. We performed a post-hoc analysis to determine if more physicians reached level of competence when patients with previous surgery for SUI were excluded, but unfortunately too little data remained to draw any substantial conclusions. It could be that some physicians begin a new treatment on patients with a low chance for cure (e.g. patients with high comorbidity), whereas others delay treatment on this patient group until they are more experienced. The fact that duration of treatment increased instead of decreased substantiates this hypothesis somewhat.

A third and last explanation for the wide distribution among outcomes is the lack of surgical standardization. PDMS-U is injected blindly without marking points that provide feedback on whether the material is placed in the theoretically optimal location. It is questionable whether the procedure is standardized enough to take anatomical variation among patients into account.

The outcomes used to define the learning curve should be carefully selected (10). As with most other learning curve studies, our study used operational variables (duration of the procedure) as well as patient outcomes (complications). We selected 'complications overall' as one of the outcomes for LC-CUSUM graphs, as we hypothesized that the occurrence of complications would decrease with growing experience. However, this outcome is very broad as it comprises many complications, which might not all be related to the physician's competence. We therefore decided to specify 'urinary retention' and 'excision' as these outcomes are more clearly defined, objectively assessed, prevalent and relevant for this specific procedure. Still, no relationship between occurrence of 'urinary retention' or 'excision' and physicians' experience

was found. The duration of the procedure as an outcome measure for bulk injection therapy PDMS-U is not optimal, as the PDMS-U procedure depends on steps that require a defined amount of time, which makes it almost impossible to decrease the procedure time.

The absence of a clear definition of competence limits the evaluation of competence (10). The level of competence is defined by the cut-off value of the (un)accepted failure rate. In this study, these cut-off values were based on literature. Changing the cut-off values would change the bandwidth of H0 and H1, which consequently would alter the conclusions drawn, i.e. more physicians would have reached competence if higher cut-off values were used. However, from a clinical perspective it is questionable whether higher cut-off values of (un)accepted failure rates are reasonable.

Our study reported an overall complication rate of 50.2% which is higher than complication rates reported in other bulking agent studies. Kocjancic *et al.* (2019) reported that 1 in 3 patients experience complications after bulking agent treatment (19). Brosche *et al*. (2021) published the long-term efficacy and safety of bulking agent Bulkamid® and reported transient prolonged emptying time (15.3%) and frequent urination (9.6%) to be the most common complications (20). It seems that exposure and excision, which were as high as 14.3% and 20.2% in our study, are more common with this type of bulking agent, most likely as the material is not as hydrophilic as for example Bulkamid®, and thus likely to generate more stress-shielding on the urethra and vagina.

To our knowledge, there are no studies on the learning curve for bulk injection therapy for SUI. Maguire et al. (2013) used CUSUM for the learning curve of six physicians learning retropubic TVT (21). This study also showed a wide inter-physician variability. For some physicians, the extrapolated reached-level-of-competence was 20 procedures, for another physician it was 50 procedures. Other studies reporting on the learning curve of MUS surgery for SUI were based on single surgeon outcomes (22-25). Spelzini *et al.* (2017) and Serati *et al*. (2015) found similar results as this study: complications following sling surgery were not influenced by the number of procedures performed (22, 23).

A limitation of this study is that some data were collected retrospectively which may have underreported the number of complications. Second, the level of supervision received, which was provided in at least three patients, was not considered. Third, there was variation in the way the technique was applied, for example in the volume of the depots, and two of the four physicians used for LC-CUSUM analysis did not use the applicator of the device when injecting the two lower depots. Finally, the sample size of this study was small: a larger sample would yield more insight into the variation in learning curves and average number of procedures needed to establish a learning curve.

To conclude, PDMS-U is associated with a considerable chance of complications which is not related to the physicians' experience. It is therefore arguable if the current training program of three supervised PDMS-U procedures is adequate. We recommend physicians to be supervised until they feel confident with the procedure and to monitor their own safety outcomes.

## CONFLICT OF INTERESTS

Jan-Paul W.P. Roovers reports consultant of Coloplast. Fenne M. Casteleijn and Rik van Eekelen have nothing to declare.

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## APPENDIX A:

The following values have been used to design the CUSUM:

**Calculation of CUSUM for overall complications**

Failure is defined as X=1; Success is defined as X=0
Acceptable failure rate is 24% (p=0.24)
Unacceptable failure is 48% (p=0.48)
Theoretical Type I and Type II error is 10% (p=0.10), what makes α and β:
(ln(0.9/0.1)=2.197
P= ln(P1/P0) = ln(12)=0.69
Q=ln(0.76/0.52)=0.38
N= pt number 1,2,3 consecutive pts
Decrement of each success is s=Q/(P+Q) = 0.38/1.07 =0.36
Increment for each failure is (1-s) = (1-0.36)= 0.64
H0 = β/(P+Q) = 2.2/1.07=-2.06
H1 = α /(P+Q) = 2.2/1.07=2.06

**Calculation of CUSUM for retention**

Failure is defined as X=1; Success is defined as X=0
Acceptable failure rate is 10% (p=0.10)
Unacceptable failure is 20% (p=0.20) (twice acceptable failure rate)
Theoretical Type I and Type II error is 10% (p=0.10), what makes α and β:
(ln(0.9/0.1)=2.19
P= ln(P1/P0) = ln(2)=0.69
Q=ln(0.90/0.80)=0.12
N= pt number 1,2,3 consecutive pts
Decrement of each success is s=Q/(P+Q) = 0.12/0.81 =0.15
Increment for each failure is (1-s) = (1-0.15)= 0.85
H0 = β/(P+Q) = 2.2/0.79=-2.72
H1 = α /(P+Q) = 2.2/0.79=2.72

**Calculation of CUSUM for excision**

Failure is defined as X=1; Success is defined as X=0
Acceptable failure rate is 11% (p=0.11)
Unacceptable failure is 22% (p=0.22) (twice acceptable failure rate)
Theoretical Type I and Type II error is 10% (p=0.10), what makes α and β:
(ln(0.9/0.1)=2.19
P= ln(P1/P0) = ln(2)= 0.69

Q=ln(0.89/0.78)=0.13
N= pt number 1,2,3 consecutive pts
Decrement of each success is s=Q/(P+Q) = 0.12/0.82 =0.15
Increment for each failure is (1-s) = (1-0.15)= 0.85
H0 = β/(P+Q) = 2.2/0.82=-2.68
H1 = α /(P+Q) = 2.2/0.82=2.68

# Chapter 

# Summary

## SUMMARY - Urethral bulk injection therapy for female stress urinary incontinence: a multiperspective evaluation

This thesis aimed to evaluate different aspects of bulking agent polydimethylsiloxane Urolastic® to understand its value as a treatment option of stress urinary incontinence, including: the patients perspective, the efficacy and safety and influence on sexual function, the physicians' learning curve and the cost-effectiveness.

**Chapter 2** is a qualitative study where through purposive sampling women with stress urinary incontinence were interviewed face-to-face, with the aim to identify all treatment decision factors that determined the preference for urethral bulk injection therapy or mid-urethral sling (MUS) surgery. After interviewing twenty patients data-saturation was reached. Sixteen treatment decision factors were identified, categorized in procedural, personal, professional, social and external factors. The general expectation towards treatment was that .women believed 'becoming dry' was wishful thinking. Major decision factors for bulk injection therapy were: minimally invasive character (no incision, no anesthesia), not worth the risk of an operation when having few complaints, no need to become dry, preserve more invasive MUS-surgery as the second option, concerns about mesh use. Major decision factors for MUS-surgery were: the higher chance of cure, one-session procedure, familiarity with the treatment and safety concerns about silicon use. Despite the lower efficacy rates of bulk injection therapy, patients indicated that they did want to be informed about bulk injection therapy as treatment option.

In **chapter 3**, a patients preference trade-off design was used to investigate patients' acceptable cure rates of PDMS-U to prefer this treatment option compared to either transobturator tension-free vaginal tape or single incision minisling. During the interview of 105 patients the cure rate of PDMS-U was decreased from 85% to 10% with steps of 2% until the patient's treatment preference switched to transobturator tension-free vaginal tape or single incision minisling. We showed that, when transobturator TVT is offered as a procedure with a 85% cure rate and performed under general anesthesia and hospital admission, patients are willing to give up 6% cure rate to prefer PDMS-U, indicating that PDMS-U must be at least 79% (interquartile range [IQR]: 69, 85) effective to be an attractive alternative treatment. When PDMS-U was compared to a single incision minisling performed under local analgesia an sedation patients, were not willing to trade cure rate for PDMS-U, indicating that PDMS-U must be at least 85% (IQR: 71, 85) effective to be preferred. Patients with longer duration of SUI symptoms were willing to trade more cure rate to prefer PDMS-U treatment (situation 1: $p = 0.02$, $r = 0.22$; situation 2: $p = 0.049$, $r = 0.19$). None of the following

patient characteristics were correlated to the treatment trade-off point: age, severity of symptoms, disease-specific quality of life, previous MUS surgery and previous anesthesia. The three most mentioned reasons to prefer MUS surgery were: fear of silicones, one-off procedure, and unfamiliarity of bulk injection therapy. For PDMS-U these were: minimal invasiveness, local analgesia and quick recovery.

In **chapter 4,** a cross-sectional study, we showed that the vast majority (85%) of the 87 patients who were treated a median of two years ago, still experienced SUI symptoms, but 51% were satisfied with the results, 62% would have done PDMS-U again and 69% would have recommended PDMS-U to some else. These satisfaction rates, as well as the subjective cure (46%), were not significantly different 0 to 12 months, 13 to 24 months or ≥25 months post-treatment. The objective cure rate (35/74 patients, 47%) however did decrease after longer time post-treatment (time-frames: 0 to 12 months, 13 to 24 months, and ≥25 months post-treatment: 77%, 56% and 35% (p=0.02)). In conclusion, patients can be satisfied while still having SUI symptoms. Safety analysis in this study showed that overall 60% encountered complications, of which urinary retention, pain and dyspareunia were most frequent. The excision rate of PDMS-U due to complications (most common were pain, exposure or erosion) was 18% and the re-injection rate was 6%. Although this cross-sectional design had its limits such as selection bias through non-responders, recall bias and collection bias (underreporting of complications), this study was the first to bring forward post-marketing risk evaluation and patients' satisfaction of PDMS-U on the long-term.

**Chapter 5** is a pilot study that evaluated the efficacy and safety of PDMS-U in patients with a poor prognostic profile for cure and who were unsuitable for MUS-surgery (i.e. recurrent SUI after surgical procedure, prior oncologic gynecological surgery, voiding problems due to neurologic disease). Of the twenty patients included we demonstrated that at six months follow-up the 18 (90%) of the 20 included patients reported subjective improvement, 56% were subjectively cured and disease specific quality of life improved significantly. One should keep in mind that the subjective improvement might include a placebo effect, since we expect from this difficult to cure women (e.g. a history of pelvic cancer) that any kind of improvement is perceived satisfying. Yet, the objective cure of 65% was higher than the subjective cure. With regards to safety, 40% had incomplete voiding after the treatment for which catheterization was necessary and 25% needed re-injection. These numbers could be considered high, but are also expected higher in this patient group. All in all, we found these results promising and we initiated a larger study with a two year follow-up including a broader selection of patients (chapter 6), with the hypothesis that efficacy rates would be higher in patients with uncomplicated SUI and re-intervention rates would be lower.

**Chapter 6** showed a non-randomized comparative two-armed cohort study of 131 patients in the PDMS-U group versus 153 in the MUS-surgery group with a cost-effectiveness analyses after one year follow-up. The subjective cure for MUS-surgery and PDMS-U were respectively: 101/112 (90%) versus 40/87 (46%), the adjusted OR (for age, BMI, severity, type of urinary incontinence and previous SUI procedure) was 4.9. The objective cure rate for MUS-surgery and PDMS-U were respectively: 98/109 (90%) versus 58/92 (63%), adjusted OR 5.4. Urinary retention and urinary tract infection were both common in the two treatment groups. Exposure of bulk material PDMS-U was prevalent in 23.6.% and excision of PDMS-U in 19.8%. Regarding the costs, we included costs of the intervention, personnel, hospital admissions, re-interventions, adverse events, specialist consultations and productivity loss. The total costs of all categories were lower in the PDMS-U group (€3,567 (95%CI: 3,168 to 4,017) for PDMS-U and €6,688 (95%CI: 6,129 to 7,283) for MUS-surgery, mean difference €3,120 (95%CI: 2,382 to 3,861)). A relative large cost item for PDMS-U was the category 're-interventions', whereas for MUS-surgery production loss was the largest cost item. Cost-effectiveness analysis was performed for disease specific quality of life (IIQ questionnaire) and for generic quality of life (EQ5D5L questionnaire). For IIQ as well as for EQ5D5L, MUS-surgery was more expensive than PDMS-U but also more effective. The incremental cost-effectiveness ratio (ICER) on IIQ scale for MUS-surgery was much lower (€15,598 (95%CI: 10,950 to 21,966)) than the ICER on EQ5D5L scale (€37,408 (95%CI: 22,817 to 67,102)). This means that, when compared to PDMS-U, one have to spend double amount for one additional QALY on generic quality of life for MUS-surgery than for one QALY on disease specific quality of life. The willingness to pay (WTP) showed also very different results between disease-specific quality of life and generic quality of life. When adjusted for baseline differences, a WTP of €25,000 for one disease-specific QoL (IIQ) QALY, MUS-surgery had the highest probability to be cost-effective (in 84%), whereas for one generic QoL (EQ5D5L) QALY, PDMS-U had the highest probability to be cost-effective (in 99%). For MUS-surgery to be the cost-effective treatment with regards to generic QoL, the WTP must be over €100,000. We performed sensitivity analysis including patients who completed baseline and 12 months follow-up for IIQ or EQ5D5L. This showed no difference in outcomes for IIQ, but the results for EQ5D5L were more in favour for PDMS-U (ICER increased from €37,408 to €47,526). Another sensitivity analysis assuming zero leave days for women in which absenteeism data was missing, showed that results were more in favour of MUS-surgery because the costs were lower compared to initial analysis (the ICERs were €12,365 (95%CI: 7823 to 18,283) for IIQ and €29,889 (95%CI: 16,777 to 56,204) for EQ5D5L).

**Chapter 7** is a secondary analysis of chapter 6 that evaluated the impact of both MUS surgery and PDMS-U on the sexual function and compared outcomes after 12 months follow-up. The validated Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire – IUGA Revised (PISQ- IR) was used to assess sexual function at baseline and after 6 and 12 months follow-up. The primary outcome was the PISQ-IR single summary score of sexually active (SA) women at 12 months follow-up. Secondary outcomes were: comparing the PISQ-IR subscale scores of SA and non-sexually active (NSA) women, the proportions of sexual activity and subjective improvement. 146 patients who underwent MUS-surgery and 113 patients who underwent PDMS-U were available for analysis. Women in de PDMS-U group were older and more often postmenopausal, used vaginal estrogen more often, more had undergone prior surgical interventions for pelvic organ prolapse or UI, fewer had a partner, and fewer were sexually active. Both MUS-surgery and PDMS-U resulted in significant increased single summary score at 12 months. After correcting for differences in baseline characteristics, the PISQ-IR summary score at 12 months was similar for both treatment groups at 6 months (MUS: 3.3 (95% CI [3.25-3.41]) vs. PDMS-U: 3.4 (95% CI [3.2-3.58])) and 12 months of FU (MUS: 3.4 (95% CI [3.35-3.51]) vs. PDMS-U: 3.5 (95% CI [3.29-3.60])). Both procedures resulted in significant improvement of condition-specific (SA-CS) and condition-impact (SA-CI) subscale scores after 6 and 12 months follow-up. After MUS-surgery the global quality subscale score significantly deteriorated, but arousal and orgasm subscale score significantly improved. With regards to NSA women, none of the subscale scores significantly changed following either procedure. To conclude, sexual function improves equally following PMDS-U and MUS surgery in sexually active women, by tackling the condition's impact on sexual activity and quality. A limitation of this study is, because of the non-randomized design, more NSA women were in the PDMS-U group. Therefore fewer of their questionnaires could be included for analysis.

**Chapter 8** is a reanalysis of three studies (chapter 4, 5, 6) on the efficacy and safety of PDMS-U to investigate the learning curve of PDMS-U. A total of nine physicians were included who performed 203 PDMS-U procedures. The primary outcome was the needed number of PDMS-U procedures to achieve acceptable failure rates with regards to: 'complications overall', 'urinary retention' and 'excision', using the LC-CUSUM method. Only physicians who performed ≥ 20 procedures were used for primary analysis. The secondary outcome was to determine if safety outcomes (complications overall, urinary retention, pain, exposure, excision of PDSM-U) and duration of treatment were related to the procedure number, using logistic and linear regression analysis. We showed that the vast majority did not reached the acceptable failure rates and thus did not achieve level of competence. Only two physicians did: one at procedure number 20 with regards to complications overall, one at procedure number

40 with regards to urinary retention. Second, none of the associations between procedure number and complications turned out statistically significant. A small but significant linear association was found between procedure number and duration of the procedure (mean difference 0.83 minutes per 10 additional procedures, 95%CI 0.16 to 1.48). The large inter-physician variability could be caused by the heterogeneity of patients. Second, the injections are done blindly without giving feedback whether the bulk material is placed in the theoretically optimal position, therefore it is questionable if the procedure is standardized enough to objectify a learning curve.

# Chapter 10

# General discussion

The European Association of Urology (EAU) recommend different surgical treatments for SUI (MUS-surgery, autologous fascia PVS, Burch colposuspension and bulk injection therapy), although there is no consensus on what is the most optimal option (1). Therefore, they encourage healthcare professionals to make choices through shared decision-making. Mid-urethral sling (MUS) surgery is very popular and the most frequently chosen treatment option among healthcare professionals (2, 3). Over the last decade, however, a negative trend for admissions for MUS-surgery occurred, since the US Food and Drug Administration (FDA) published a public health notification regarding the safety of vaginal mesh for the treatment of pelvic organ prolapse (POP) in 2011 (3). This had led to an increase in reported patient-perceived mesh complications and a huge number of patients filed product liability claims (4, 5). As a result, the National Health Service (NHS) in England announced a national discontinuation of mesh for the treatment of POP and SUI in 2018 (6). Since, POP-surgery and MUS-surgery is being scrutinized over polypropylene mesh-related complications such as vaginal exposure, extrusion and pain (4). Recently (February 2023), the Federation of Gynecology and Obstetrics (FIGO) published their recommendations of the use of MUS-surgery and concluded that it is a safe and effective treatment option (7).

Bulk injection therapy show inferior cure rates to other surgical therapies, but it is perceived as an appealing option because of its associated low morbidity, office-based procedure, relatively quick recovery, and the option of undergoing MUS-surgery if the results aren't satisfactory. In the past, bulk injection therapy have had limited utility and was indicated for patients with intrinsic sphincter deficiency (ISD). Later on, studies showed that bulking agents are also efficacious in patients with urethral hypermobility (8, 9). Nowadays, bulk injection therapy is widely implemented and the indications have expanded to patients who did not benefit from surgical intervention, who have a contra-indication for anesthesia, who wish to avoid mesh, to even a possible first-line treatment. Yet, the exact indication is still unclear. There are currently many different bulking agents available, not all of which are well researched and with varying clinical outcomes. Moreover, still little is known for whom bulk injection therapy is most beneficial. We aimed for a total clinical evaluation of a bulking agent to be able to say more about the indication. We have opted for a relatively new bulking agent that distinguishes itself from other bulking agents. Polydimethylsiloxane Urolastic® (PDMS-U) is injected blindly around the urethra and then takes a final form, which is no longer absorbed by the body. Because most other bulking agents are (partly) absorbed by the body, repeated injections are a well-known phenomenon. This relevant difference hypothetically results in PDMS-U being more effective in the long term and requiring fewer repeated injections. Before the start of this thesis, two cohort studies had been conducted with a total of 125 participants, which showed encouraging results with objective cure rates of 59-68% and significant improvement in quality of life (10,

11). Our aim was to further evaluate the efficacy, safety and effect on sexual function through a high power post-market clinical follow-up study and demonstrate the value of PDMS-U economically and from the patients' perspective. Lastly, we analyzed to what extent the physicians learning-curve influenced safety outcomes.

**Patients' perspective of bulking agent PDMS-U**

In **chapter 2** we demonstrated that patients have diverse expectations when it comes to surgical treatment for SUI: some patients have very specific goals (e.g. 'playing field hockey again'), some only expect improvement of symptoms, while others expect to become totally dry. This wide range of patients' goals are also shown in other (qualitative) preference studies on SUI therapy (12-15). Furthermore**, chapter 2** showed that many factors are involved in the choice between bulking agent and mid-urethral sling surgery. Although procedural factors such as efficacy, complications, type of anesthesia were often decisive in treatment selection, familiarity with the treatment, previous experience of surgery, advise from social contacts and expertise of the physician were also important. As a result, it appeared that some patients prefer bulk injection therapy despite the lower effectiveness.

Regardless of the patient's treatment preference, they all found it important that they could choose between treatments and that both treatments (bulk injection therapy and MUS-surgery) were presented. In **chapter 3** we showed that when patients could choose between bulk injection therapy and MUS-surgery, they were willing to sacrifice only little effectiveness for bulk injection therapy. Namely, a median of 6% when compared to trans-obturator MUS-surgery to avoid hospitalization and general/spinal anesthesia and 0% when MUS-surgery was proposed as a treatment performed in a daycare setting under local analgesia (presented as single incision mini-sling). This means that the efficacy of bulk injection therapy must be 79-85% to be the first preferred surgical option for SUI by the majority of patients. A limitation of **chapter 3** is that the hypothetically used re-injection rate of 20% was much higher than shown in the clinical studies, namely 4.6%. And the opposite turned out for excision of bulk material; while in the preference study the rate of excision was not mentioned, later in clinical studies it turned out to be considerably high at 19.6%. Thus it is likely that this would have an influence on the results. The results of this chapter are therefore more generalizable for other bulking agents than for PDMS-U specifically.

So from a patient perspective, PDMS-U has a place in the treatment of SUI, although most will opt for MUS surgery since its efficacy is much higher. During shared decision-making, exploring the patients' perception, personal goals and expectations towards treatment for SUI is of great importance. This can certainly be improved in daily practice, by international guidelines and in decision aids. Shared-decision is more focused on providing procedural information, the efficacy and complications, rather

than taking into account the patients personal goals and previous experiences. The "fundamental principles of shared-decision making" by the EAU guideline provides an eight point overview how to perform shared decision-making, but does not include to explore the patients expectations or goals. Also the patient decision aids only describe procedural factors and does not take into account the personal factors (1, 16).

**Clinical perspective of bulking agent PDMS-U**

We evaluated the efficacy and safety of PDMS-U in three studies: a cross-sectional study in patients being treated with PDMS-U (**chapter 4**), a pilot study in patients with a poor expected surgical outcome (**chapter 5**) and finally in a prospective comparative cohort study with MUS-surgery where one year follow-up results were presented (**chapter 6**). These studies investigated the efficacy and safety in a mixed population including patients with uncomplicated SUI, in patients with previous failed surgery, patients with comorbidity that have contra-indications for MUS-surgery and the elderly. In other words, a reflection of the various perceived indications of bulk injection therapy. These studies showed that the subjective cure rate of PDMS-U lies between 46-56% and the objective cure rate between 47-65%, but does seem to decrease over time. The vast majority of patients treated over two years ago still experienced SUI symptoms, however, 51% were satisfied with the results, 62% would have done PDMS-U again, and 69% would have recommended PDMS-U to someone else (**chapter 4**).

Although direct comparative studies are lacking, PDMS-U does not seem superior to other bulking agents for short-term efficacy. When compared to bulking agent PAHG Bulkamid®, the objective cure rate is comparable with PDMS-U. Results at twelve months of the latest randomized controlled trial (RCT) of Bulkamid® versus MUS-surgery showed an objective cure rate of 66.4%. The subjective cure rate of PAHG Bulkamid® was lower than PDMS-U, namely 23.4%. However, stricter Likert scales and cut-off values were used compared to our studies. The median satisfaction score was 85 (IQR 65-98), which is higher than the patient satisfaction score of PDMS-U (51%, **chapter 4**) (17). When comparing PDMS-U with bulking agent Macroplastique™, Hoe *et al*. showed that the overall success rate of twenty-three studies varied from 48% to 84% (total n = 1083), which is somewhat higher than PDMS-U (18).

The success rates of PDMS-U are lower than clinical outcomes of MUS-surgery (**chapter 6**) or other surgical methods. This is in line with a systematic review and meta-analysis of bulking agents (polyacrylamide hydrogel injection, Bulkamid®, Macroplastique®, Contigen®, Coaptite®, and collagen injections) versus other surgical methods that showed bulking agents were less effective in subjective improvement (RR = 0.70, 95% CI: 0.53 to 0.92, p = 0.01). Objective outcome measures were too diverse for a meta-analysis (19). Retropubic and transobturator mid-urethral slings are the most effective surgical option, with subjective cure rates of 62% to 98% for the

transobturator approach and 71% to 97% for retropubic approach (20-22), although a recent RCT showed non-inferiority for single-incision mid-urethral sling surgery (SIMS) (23). Gaddi *et al*. showed that even repeat MUS-surgery still yields lower failure rates compared to bulk injection therapy (OR 3.49, 95% CI 1.34–9.09, $p = 0.01$) (24).

With regards to safety, urinary retention is the most common complication for PDMS-U with prevalence rates of 21-40%, followed by exposure (5-24%), urinary tract infection (0-15%), pain (0-15%) and dyspareunia (0-15%). Chance of excision of PDMS-U is 18-20%. Re-injection is indicated at 4.6-25%. The range of these adverse events are wide, which is probably a result of the different study designs or a small power. The most accurate prevalence rates would therefore be the outcomes of our multicenter, prospective cohort study (**chapter 6**). It is still unknown in which patients pain, exposure and excision are more prevalent. Subgroup analysis of the two year follow-up of **chapter 6** will give some insight on this matter. Compared to PAHG Bulkamid® and Macroplastique®, PDMS-U is associated with a higher risk of pain, dyspareunia, exposure and excision, while urinary tract infection and re-injection are less common (18).

With regards to the impact on sexual function, **chapter 7** showed that PDMS-U has a positive influence on the sexual function. In sexually active patients, the condition-specific and condition-impact subscale scores significantly improved and none of subscales deteriorated. This implies that the decrease in SUI symptoms reduces fear and shame around sexual activity and improves sexual quality. For non-sexually active patients, the subscales did not improve after PDMS-U or MUS-surgery and they remained sexually inactive, thus improvement in SUI symptoms did not result in a change in sexual activity. So all in all, it can be communicated to sexually active patients considering PDMS-U that, with respect to sexual function, this is a safe and effective treatment option. As for the other bulking agents, only PAHG Bulkamid® has been studied and similar positive results were seen (25). Remarkable is the fact that although dyspareunia, pain and exposure are common for PDSM-U, this does not seem to affect the sexual quality significantly. This topic could be further researched: what is the long term impact of PDMS-U on sexual function term in patients experiencing dyspareunia, pain or exposure after the procedure?

The relation between prevalence of complications or excision and the physicians expertise was studied in **chapter 8**. We showed that safety outcomes between physicians differ substantially, but the amount of expertise did not influence safety outcomes. So a higher expertise did not result in less complications. This was an unexpected outcome. It seems that the occurrence of complications and excision is more dependent on other factors. One of those factors could be the position of the bulk material. PDMS-U is blindly injected, therefore physicians are unable to see if the bulk material is placed in the optimal anatomic position. An imaging study with CT-scans

after PDMS-U procedure showed that the shape and position of the bulk material appears to be variable: 45% were not placed at the intended mid-urethral position and in only 40% the material was distributed circumferentially. However, this study showed that subjective outcome and complications such as pain were not related with the position of the bulk material (26). So, why does some patients experience pain or exposure and are indicated for excision while others are not? This question remains unanswered, but would be very valuable to know, since these negative outcomes greatly determine the exact indication for PDMS-U for SUI. We recommend therefore that physicians who perform this intervention should monitor their own safety outcomes.

**Health-economic perspective of PDMS-U**

It is clear that health care costs are rising (27). With an aging population, urinary incontinence is expected to increase substantially — the need for cost-effective treatments is clear. Cost-analysis with a 10-year or life-long time horizon showed that retropubic mid-urethral sling was the most cost-effective option. Alternatives are either more invasive or less effective (28). For bulk injection therapy, the literature shows a wide range in costs leading to inconclusive results. One study concluded that MUS-surgery was too expensive and therefore bulk injection therapy was the most cost-effective option (29), whereas another study showed that bulk injection therapy was more costly than MUS-surgery (30). Our study, **chapter 5,** showed that MUS-surgery is more effective but also more expensive compared to PDMS-U. Depending on the outcome measure, MUS-surgery was the most cost-effective treatment option in improving disease specific QoL, whereas PDMS-U was more cost-effective in improving generic quality of life.

For insurance companies and policy makers, PDMS-U could be an appealing therapy since our study showed that it will cost >100.000 euro for MUS-surgery to yield more net benefit in improving generic quality of life. This means, costs can be saved if PDSM-U would be offered as first surgical treatment option, and MUS-surgery is kept as an alternative, in reserve so to speak, for patients who do not benefit from PDMS-U. A cost-effectiveness analysis with a longer follow-up is needed to draw such hard conclusions. Additionally, as an alternative to both, SIMS has showed to be well-tolerated under local anesthesia and be as effective as other mid-urethral slings, which could result in being more cost-effective than PDMS-U (23).



**Implications for clinical practice**

International guidelines include bulk injection therapy, next to MUS-surgery, autologous fascial sling and colposuspension as primary treatment modality to all patients who are considering surgery for SUI. We showed that patients indeed want to be informed about bulk injection therapy as primary treatment option. Although the majority of patients will opt for MUS-surgery because of its higher cure rates, still some patients

prefer bulk injection therapy as primary treatment option because for example its less invasive character, or the reluctance to mesh. During shared-decision making we advise physicians to focus on the patients' goals and perspectives, next to the procedural information and clinical outcomes. Finally, we recommend to add 'exploring the patient treatment goal and personal perspectives' to the recommendations of the EAU guideline and shared-decision making process of the available option grids.

International guidelines state that there is no recommendation to use one bulking agent over another. This implies that every CE or FDA approved bulking agent can be offered to patients with SUI as primary surgical treatment, including PDMS-U. Yet, there are no randomized trials that directly compared existing bulking agents. Currently there are six different bulking agents on the market, of which poly-dimethyl-siloxane macro particles (Macroplastique™) and polyacrylamide hydrogel injection (PAHG) (Bulkamid®) have been evaluated most extensively, including RCTs comparing surgical modalities and clinical data up to seven years follow-up (17, 31, 32).

When we compare the clinical outcomes of PDMS-U to other bulking agents, this thesis showed that PDMS-U is associated with considerable high rates of pain, exposure and excision which is not seen in other bulking agents, while efficacy rates seem not superior. The success rates at one year follow-up were around 50% while one out of five patients were indicated for excision of the bulk material. It is unknown if complications such as pain have a potential chronic character and if the symptoms of pain disappear after excision of the bulk material. Moreover, it is unknown what the consequences of excision are for the effectiveness. In addition, there are hardly any results of PDMS-U over two years follow-up. So at the moment the data is too premature to fully inform patients about the long-term effectiveness and safety of PDMS-U. It is clear that patient safety is of paramount importance, since MUS-surgery continues to be scrutinized over the risk of erosion and pain, which is shown in a systematic review to be as low as 1.9% and 0.6 % respectively (33). Given that there are bulking agents available that have been more extensively researched without the occurrence of erosion or exposure, we therefore think PDMS-U should not be offered as a primary treatment option at this moment. This would be different if, in the future, it turns out that the long term safety are non-inferior or if the efficacy is superior to other bulking agents.

For the treatment of recurrence/persistent SUI, a different consideration can be made. In patients who have already undergone surgeries for SUI, it may be that they appreciate a bulking agent with a one-off procedure more, despite the risk for exposure and pain, than a bulking agent with a higher chance of re-injection. This thesis showed that PDMS-U could be a valuable treatment option for patients with high comorbidity or a contra-indication for MUS-surgery, although the sample size was small. In addition, PDMS-U might also be beneficial for patients who have undergone

previous surgery for SUI. In our cross-sectional study, higher objective cure rates for patients with previous surgery (61% vs 37%; p = 0.04) was found. Subgroup analysis of two years follow-up results of **chapter 6** will give more insight into success rates for patients with previous failed surgery. The benefit in this subgroup was not observed in a retrospective case series of PAHG Bulkamid® and Macroplastique™ (34). It may be that the non-absorbable property of PDMS-U shows its benefit in this subgroup of patients.

When PDMS-U is offered as treatment option, physicians are able to inform patients better about the efficacy, safety and re-intervention rate because of this post-market evaluation thesis. It should clearly mentioned that complications are common and at a minimum patients should be notified about the chance of urinary retention, exposure, urinary tract infection, pain and dyspareunia. Additionally, it should be communicated that the excision rate of PDMS-U is 18-20% and is higher than other bulking agents, whereas re-injections are less often indicated (4.6-25%) compared to other bulking agents. We recommend that physicians who perform PDMS-U procedures monitor their outcomes for post-market surveillance. A profound network of the participating centers should be formed and results should be transparently communicated in order to determine if centralization of patients is necessary.

**Implications for further research**

Long-term post-market surveillance and studies on the occurrence of pain, exposure and re-interventions of PDMS-U are necessary to avoid controversy as was seen with mesh use. If it turns out that re-intervention rates decrease and success rates are stable, then the main reason for PDMS-U could be to avoid re-injections and thus be more cost-efficient bulking agent in the long run.

Future research should focus on comparing and improving existing bulking agents rather than introducing new bulking agents, to identify their flaws and improve them. Hence, profound questions must be answered: why and to whom does erosion/excision occur? Which patients do not benefit from bulk injection therapy and why? It can turn out that there is no ‘one size fits all’ bulking agent and treatment selection or bulking agent selection is based upon personalized prediction models. The government can stimulate, finance and facilitate investigation on optimizing existing medical devices, instead of using new devices as part of structured research programs.

There is potential to further develop PDMS-U to make the most effective use of this product. The optimization process of the product may start by improving the injection technique, for example to visualize injection, to avoid erosion to the urethra or bladder or exposure through the vaginal wall. Second, the volume and shape of the depots vary significantly and it is unknown what must be the most optimal volume, shape or position. If the position, volume and shape of the bulk material could be objectified

during the procedure, there might be more insight on understanding the reasons for the different learning curves.

Third, to further determine the indication of PDMS-U it would be helpful to set up a (randomized) study comparing PDMS-U versus PAHG Bulkamid® in patients with recurrence/persistent SUI after surgery.

Altogether, the contribution of this thesis is the collection of post-market follow-up data on the wide use of PDMS-U and subsequently evaluating PDMS-U from multiple viewpoints, giving insight into the patient's perspective, efficacy, safety, cost-effectiveness, influence on sexual function and physician's learning curve. The collected data are partly generalizable for other bulking agents, but partly not due to the specific material properties of PDMS-U. These outcomes will likely be of interest to several stakeholders, including patients, physicians, guidelines and insurance companies to decide on treatment for patients who experience SUI.

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# Appendices

## NEDERLANDSE SAMENVATTING

Dit proefschrift was gericht op het evalueren van verschillende aspecten van bulkinjectietherapie polydimethylsiloxaan Urolastic® om de waarde ervan te begrijpen als een behandelingsoptie van stress-urine-incontinentie, waaronder: het perspectief van de patiënt, de werkzaamheid, de veiligheid en kosteneffectiviteit, de invloed op de seksuele functie en de leercurve van de arts.

**Hoofdstuk 2** is een kwalitatieve studie waarbij door middel van doelgerichte steekproeven vrouwen met stress-urine-incontinentie face-to-face werden geïnterviewd, met als doel alle factoren voor de behandeling te identificeren die bepalend waren voor de voorkeur voor bulkinjectietherapie of mid-urethrale sling (MUS) operatie. Na het interviewen van twintig patiënten werd dataverzadiging bereikt. Zestien behandelbeslissingsfactoren werden geïdentificeerd, gecategoriseerd in procedurele, persoonlijke, professionele, sociale en externe factoren. Over het algemeen hadden vrouwen ijdele hoop dat ze volledig droog werden. Belangrijke beslissingsfactoren voor bulkinjectietherapie waren: het minimaal invasieve karakter (geen incisie, geen verdoving), de risico's van een operatie zijn het niet waard bij weinig klachten, geen noodzaak om droog te worden, een invasievere operatie als tweede optie behouden, zorgen over veiligheid van mesh gebruik. Belangrijke beslissingsfactoren voor MUS-chirurgie waren: de hogere kans op genezing, procedure betreft maar één sessie, bekendheid met de behandeling en veiligheidsproblemen met betrekking tot siliconengebruik bij bulkinjectietherapie. Ondanks de lagere werkzaamheidspercentages van bulkinjectietherapie gaven patiënten aan wel geïnformeerd te willen worden over bulkinjectietherapie als behandeloptie.

**Hoofdstuk 3** is een patiënten preferentie studie met als doel om de aanvaardbare genezingskans van PDMS-U bij patiënten met SUI te onderzoeken in vergelijking met ofwel een transobturator tape of minitape. Er werden 105 patienten geïnterviewd. Tijdens het interview werd de genezingskans van PDMS-U verlaagd van 85% naar 10% met stappen van 2% totdat de voorkeur van de patiënt voor behandeling overging op transobturator tape of minisling. We toonden aan dat wanneer transobturator tape wordt aangeboden als een procedure met een genezingspercentage van 85% en wordt uitgevoerd onder algemene anesthesie met een ziekenhuisopname, patiënten bereid zijn om 6% genezingspercentage op te geven om de voorkeur te geven aan PDMS-U. Dit geeft aan dat PDMS-U minimaal 79% (interkwartielbereik [IQR]: 69, 85) effectief moet zijn om een aantrekkelijke alternatieve behandeling te zijn. Wanneer PDMS-U werd vergeleken met een minisling die werd uitgevoerd onder lokale analgesie en sedatie zonder overnachting in het ziekenhuis, waren patiënten niet bereid

om het genezingspercentage in te leveren voor PDMS-U. Dit geeft aan dat PDMS-U ten minste 85% (IQR: 71, 85) effectief moet zijn om voorkeursbehandeling te zijn ten opzichte van de minisling. Patiënten met een langere duur van SUI-symptomen waren bereid meer genezingspercentage in te ruilen voor PDMS-U-behandeling (situatie 1: p = 0.02, r = 0.22; situatie 2: p = 0.049, r = 0.19). Andere patiëntkarateristieken (leeftijd, ernst van symptomen, ziekte specifieke kwaliteit van leven, eerdere MUS-operatie en eerdere ervaring met anesthesie) waren niet gecorreleerd aan het afkappunt van genezingskans. De drie meest genoemde redenen om de voorkeur te geven aan MUS-operatie waren: angst voor siliconen, eenmalige procedure en onbekendheid met bulkinjectietherapie. Voor PDMS-U waren dit: minimaal invasief, lokale analgesie en snel herstel.

In **hoofdstuk 4**, een cross-sectionele studie, toonden we aan dat de overgrote meerderheid (85%) van de 87 patiënten die gemiddeld twee jaar geleden werden behandeld, nog steeds SUI-symptomen ervoer, maar 51% tevreden was met de resultaten, 62% PDMS-U opnieuw zou hebben gedaan en 69% PDMS-U aan iemand anders zou hebben aanbevolen. Deze tevredenheidscijfers, evenals de subjectieve genezing (46%), waren niet significant verschillend van 0 tot 12 maanden, 13 tot 24 maanden of ≥25 maanden na de behandeling. De objectieve genezingskans (47%, n=35 van de 74 patiënten) nam echter af na een langere tijd na de behandeling (termijnen: 0 tot 12 maanden, 13 tot 24 maanden en ≥25 maanden na de behandeling: 77 %, 56% en 35% (p=0,02)). Concluderend, patiënten kunnen tevreden zijn met PDMS-U terwijl ze nog steeds SUI-symptomen hebben. Veiligheidsanalyse in deze studie toonde aan dat in totaal 60% complicaties ondervond, waarvan urineretentie, pijn en dyspareunie het meest frequent waren. Het excisiepercentage van PDMS-U als gevolg van complicaties (de meest voorkomende waren pijn, blootstelling van het bulkmateriaal of erosie) was 18% en het percentage herinjecties was 6%. Hoewel dit cross-sectionele ontwerp zijn beperkingen had, zoals selectiebias door non-responders, recall-bias en collection-bias (onderrapportage van complicaties), was deze studie de eerste die post-marketing risico-evaluatie en de tevredenheid van patiënten met PDMS-U naar voren bracht op de lange termijn.

**Hoofdstuk 5** is een pilotstudie die de werkzaamheid en veiligheid van PDMS-U evalueerde bij patiënten met een slecht prognostisch profiel voor genezing en die niet geschikt waren voor MUS-operatie (d.w.z. eerdere chirurgische ingrepen voor SUI, voorafgaande oncologische gynaecologische chirurgie, mictieproblemen als gevolg van neurologische aandoening). Van de twintig geïncludeerde patiënten toonden we aan dat na zes maanden follow-up 18 (90%) van de 20 geïncludeerde patiënten subjectieve verbetering rapporteerden, 56% subjectief genezen was en de ziekte

specifieke kwaliteit van leven significant verbeterde. Men moet in gedachten houden dat de subjectieve verbetering een placebo-effect kan omvatten, aangezien we van deze moeilijk te genezen vrouwen (bijvoorbeeld een voorgeschiedenis van kanker in het kleine bekken) verwachten dat elke vorm van verbetering als bevredigend wordt ervaren. Toch was de objectieve genezing van 65% hoger dan de subjectieve genezing. Met betrekking tot de veiligheid had 40% urineretentie na de behandeling waarvoor katheterisatie nodig was en 25% ondervond herinjectie. Deze aantallen kunnen als hoog worden beschouwd, maar worden ook hoger verwacht in deze patiëntengroep. Al met al vonden we deze resultaten veelbelovend en we startten een grotere studie met een follow-up van twee jaar met een bredere selectie van patiënten (hoofdstuk 6), met de hypothese dat de werkzaamheid hoger zouden zijn bij patiënten met ongecompliceerde SUI en re-interventiepercentages lager zouden zijn.

**Hoofdstuk 6** toonde een niet-gerandomiseerde vergelijkende tweearmige cohortstudie van 131 patiënten in de PDMS-U-groep versus 153 in de MUS-operatie groep met een kosteneffectiviteitsanalyse na een jaar follow-up. De subjectieve genezing van MUS-operatie en PDMS-U was respectievelijk: 101/112 (90%) versus 40/87 (46%), de aangepaste OR (voor leeftijd, BMI, ernst, type urine-incontinentie en eerdere SUI-procedure) was 4,9. Het objectieve genezingskans voor MUS-chirurgie en PDMS-U was respectievelijk: 98/109 (90%) versus 58/92 (63%), gecorrigeerd OR 5,4. Wat de kosten betreft, hebben we de kosten van de interventie, personeel, ziekenhuisopnames, herinterventies, bijwerkingen, specialistische consulten en productiviteitsverlies meegerekend. De totale kosten van alle categorieën waren lager in de PDMS-U-groep (€3.567 (95%CI: 3.168 tot 4.017) voor PDMS-U en €6.688 (95%CI: 6.129 tot 7.283) voor MUS-operatie, gemiddeld verschil € 3.120 (95%CI: 2.382 tot 3.861)). Een relatief grote kostenpost voor PDMS-U was de categorie 'her-interventies', terwijl voor MUS-operatie productieverlies de grootste kostenpost was. Kosteneffectiviteitsanalyse werd uitgevoerd voor ziektespecifieke kwaliteit van leven (IIQ-vragenlijst) en voor generieke kwaliteit van leven (EQ5D5L-vragenlijst). We hebben aangetoond dat zowel voor IIQ als voor EQ5D5L MUS-operatie duurder was dan PDMS-U, maar ook effectiever. De ICER op IIQ-schaal voor MUS-operatie was veel lager (€ 15.598 (95% CI: 10.950 tot 21.966)) dan de ICER op EQ5D5L-schaal (€ 37.408 (95% CI: 22.817 tot 67.102)). Dit betekent dat, in vergelijking met PDMS-U, men het dubbele bedrag moet uitgeven aan één extra QALY voor generieke kwaliteit van leven voor MUS-operatie dan voor één extra QALY voor ziekte specifieke kwaliteit van leven. De betalingsbereidheid liet ook zeer verschillende resultaten zien tussen ziekte specifieke kwaliteit van leven en generieke kwaliteit van leven. Gecorrigeerd voor baselineverschillen, had een betalingsbereidheid van € 25.000 voor één QALY op basis van ziekte specifieke kwaliteit van leven (IIQ), MUS-operatie de grootste kans om kosteneffectief te zijn (in

84%), terwijl voor één QALY op basis van generieke kwaliteit van leven (EQ5D5L), PDMS-U had de grootste kans om kosteneffectief te zijn (in 99%). Om MUS-operatie de kosteneffectieve behandeling te laten zijn met betrekking tot generieke kwaliteit van leven, moet de betalingsbereidheid hoger zijn dan € 100.000. We voerden een gevoeligheidsanalyse uit met inbegrip van patiënten die de baseline en 12 maanden follow-up voor IIQ of EQ5D5L voltooiden. Dit toonde geen verschil in uitkomsten voor IIQ, maar de resultaten voor EQ5D5L waren meer in het voordeel van PDMS-U (ICER steeg van € 37.408 naar € 47.526. Een andere gevoeligheidsanalyse uitgaande van nul verlofdagen voor vrouwen waarbij verzuimgegevens ontbraken, toonde aan dat de resultaten meer in het voordeel waren van een MUS-operatie omdat de kosten lager waren in vergelijking met de initiële analyse (de ICERs waren €12.365 (95%CI: 7823 tot 18.283) ) voor IIQ en €29.889 (95%CI: 16.777 tot 56.204) voor EQ5D5L).

**Hoofdstuk 7** is een secundaire analyse van hoofdstuk 6 die de impact van zowel MUS-operatie als PDMS-U op de seksuele functie evalueerde en uitkomsten vergelijkt na 12 maanden follow-up. Er werd een gevalideerde vragenlijst gebruikt (Pelvic Organ Prolaps/Urine-incontinentie Sexual Function Questionnaire – IUGA Revised (PISQ-IR)) om de seksuele functie te beoordelen bij baseline en na 6 en 12 maanden follow-up. De primaire uitkomstmaat was de PISQ-IR totaalscore van seksueel actieve (SA) vrouwen na 12 maanden follow-up. Secundaire uitkomsten waren: het vergelijken van de PISQ-IR-subschaalscores van SA- en niet-seksueel actieve (NSA) vrouwen, de verhoudingen van seksuele activiteit gedurende follow-up en subjectieve verbetering. 146 patiënten die een MUS-operatie ondergingen en 113 patiënten die PDMS-U ondergingen waren beschikbaar voor analyse. Vrouwen in de PDMS-U-groep waren ouder en vaker postmenopauzaal, gebruikten vaker vaginaal oestrogeen crème, hadden vaker eerder chirurgische ingrepen ondergaan voor verzakking van het bekkenorgaan of urine incontinentie, hadden minder een partner en waren minder seksueel actief. Zowel MUS-operatie als PDMS-U resulteerden in een significant verhoogde totaalscore na 12 maanden. Na correctie voor verschillen in baselinekenmerken, was de PISQ-IR-samenvattingsscore na 12 maanden vergelijkbaar voor beide behandelingsgroepen na 6 maanden (MUS: 3,3 (95% BI [3,25-3,41]) vs. PDMS-U: 3,4 (95% BI [3.2-3.58])) en 12 maanden FU (MUS: 3.4 (95% BI [3.35-3.51]) vs. PDMS-U: 3.5 (95% BI [3.29-3.60])). Beide procedures resulteerden in een significante verbetering van conditiespecifieke (SA-CS) en conditie-impact (SA-CI) subschaalscores na 6 en 12 maanden follow-up. Na een MUS-operatie verslechterde de globale kwaliteit subschaalscore significant, maar de subschaalscore voor opwinding en orgasme verbeterde significant. Met betrekking tot NSA-vrouwen veranderde geen van de subschaalscores significant na beide procedures. Concluderend, de seksuele functie verbetert in gelijke mate na PMDS-U en MUS-operatie bij seksueel actieve vrouwen, voornamelijk door verbetering

in impact van de SUI op seksuele activiteit en seksuele kwaliteit. Een beperking van deze studie is dat er vanwege de niet-gerandomiseerde opzet meer NSA-vrouwen in de PDMS-U-groep zaten. Daarom konden minder van hun vragenlijsten worden opgenomen voor analyse.

**Hoofdstuk 8** is een re-analyse van drie studies (hoofdstuk 4, 5, 6) naar de werkzaamheid en veiligheid van PDMS-U om de leercurve van PDMS-U te onderzoeken. In totaal werden negen artsen geïncludeerd die 203 PDMS-U-procedures uitvoerden. De primaire uitkomstmaat was het benodigde aantal PDMS-U-procedures om aanvaardbare faalpercentages te bereiken met betrekking tot: 'complicaties in het algemeen', 'urineretentie' en 'excisie', met behulp van de LC-CUSUM-methode. Voor de primaire analyse werden alleen artsen gebruikt die ≥ 20 procedures uitvoerden, dit waren vijf artsen. De tweede uitkomstmaat was de relatie tussen de veiligheidsuitkomsten (algemene complicaties, urineretentie, pijn, exposure, excisie van PDSM-U) en duur van de behandeling en het procedurenummer, met behulp van logistische en lineaire regressieanalyse. We toonden aan dat de overgrote meerderheid de aanvaardbare faalpercentages niet bereikte en dus geen competentieniveau bereikte. Slechts twee artsen deden dat: één bij procedure nummer 20 met betrekking tot complicaties in het algemeen, één bij procedure nummer 40 met betrekking tot urineretentie. Ten tweede bleek geen van de associaties tussen het aantal procedures en complicaties statistisch significant. Er werd een kleine, maar significante lineaire associatie gevonden tussen het aantal procedures en de duur van de procedure (gemiddeld verschil 0,83 minuten per 10 aanvullende procedures, 95% BI 0,16 tot 1,48). De grote variabiliteit in uitkomsten tussen artsen kan worden veroorzaakt door de heterogeniteit van patiënten. Ten tweede, de injecties worden blindelings gedaan zonder feedback te geven of het bulkmateriaal in de theoretisch optimale positie wordt geplaatst, daarom is het de vraag of de procedure voldoende gestandaardiseerd is om een leercurve te objectiveren.

## ABBREVIATIONS

| | |
|---|---|
| AVS | Autologous pubovaginal sling |
| AFS | Autologous fascial sling |
| BMI | Body mass index |
| CE | Conformité Européenne |
| CEA | Cost effectiveness analysis |
| CEAC | Cost-Effectiveness Acceptability Curve |
| CI | Confidence interval |
| COREQ | Criteria for reporting qualitative research |
| CST | Cough stress test |
| EAU | European association of urology |
| EQ5D5L | Euro-QoI five-dimensional measure of generic QoL |
| FDA | Food and Drug Administration |
| FU | Follow-up |
| ICER | Incremental cost-effectiveness ratio |
| ICIQ-SF | International Consultation on Incontinence Questionnaire Short Form |
| IIQ | Incontinence impact questionnaire |
| IQR | Interquartile range |
| ISD | Intrinsic sphincter deficiency |
| IUGA | International urogynaecological association |
| LC-CUSUM | Cumulative summation for the learning curve |
| MANCOVA | Multivariate analysis of covariance |
| MUI | Mixed urinary incontinence |
| MUS | Mid-urethral sling |
| NHS | National Health Service |
| NICE | National Institute for Health and Clinical Excellence |
| NSA | Non-sexually active |
| NSA-CI | Non-sexually active condition impact |
| NSA-CS | Non-sexually active condition-specific |
| NSA-GQ | Non-sexually active global quality |
| NSA-PR | Non-sexually active partner-related |
| OR | Odds ratio |
| PBI | Peri-urethral bulk injection |
| PAHG | Polyacrylamide hydrogel |
| PDMS-U | Polydimethylsiloxane-Urolastic |
| PFMT | Pelvic floor muscle training |
| PGI-I | Global impression of improvement |

| | |
|---|---|
| PGI-S | Global impression of severity |
| PISQ-IR | Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire – IUGA Revised |
| POP-Q | Pelvic organ prolapse quantification |
| PVR | Post-void residual |
| QALY | Quality-adjusted life year |
| QoL | Quality of life |
| R-TVT | Retropubic tension free vaginal tape |
| SA | Sexually active |
| SA-AO | Sexually active arousal, orgasm |
| SA-CI | Sexually active condition-specific impact |
| SA-CS | Sexually active condition-specific |
| SA-D | Sexually active desire |
| SA-GQ | Sexually active global quality |
| SA-PR | Sexually active partner-related |
| SD | Standard deviation |
| SIMS | Single incision mid-urethral sling |
| SMUS | Standard mid-urethral sling |
| SPSS | Statistical Package for the Social Sciences |
| SSQ | Surgical satisfaction questionnaire |
| SUI | Stress urinary incontinence |
| TOT | Transobturator tape |
| TVT | Tension-free vaginal tape |
| TVT-O | Tension-free vaginal tape obturator |
| UBA | Urethral bulking agent |
| UDI | Urinary Distress Inventory |
| UI | Urinary incontinence |
| US | United States |
| UTI | Urinary tract infection |
| WTP | Willingness to pay |

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**Chapter 2**

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**Chapter 3**

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**Chapter 4**

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**Chapter 5**

CK, JR were responsible for the study design and protocol. CK and HE were responsible for data collection. CK and SZ were responsible for analyzing data. CK and FC were responsible for drafting the paper. All authors contributed and approved the final version of the paper.

**Chapter 6**

JP and FC were responsible for the study design and protocol. FC was responsible for the overall logistical aspect of the study, data collection and drafted the paper. AV was responsible for data collection and drafted the paper. HE, CK were responsible for data collection and revising the paper. RE was responsible for analyzing data. JR, RE and YL were responsible for revising the paper. All authors contributed and approved the final version of the paper.

**Chapter 7**

FC, SZ and JP were responsible for the study design and protocol. FC and YL were responsible for the data collection. YL and SZ were responsible for analyzing data. YL drafted the paper. FC, JP, SZ were responsible for revising the paper. All authors contributed and approved the final version of the paper.

**Chapter 8**

JP, FC and RE were responsible for the study design. FC, YL were responsible for data collection, analyzing data and drafting the paper. RE was responsible for analyzing data. All authors contributed and approved the final version of the paper.

## LIST OF PUBLICATIONS

Schellart RP, **Casteleijn FM**, Dijkgraaf MGW, Tutolo M, Roovers JWR. Are patients willing to trade cure rate against less pain? Patients' preferences for single incision midurethral sling or transobturator standard midurethral sling. Neurourol Urodyn. 2017 Apr;36(4):1187-1193. doi: 10.1002/nau.23093

Kowalik CR, **Casteleijn FM**, van Eijndhoven HWF, Zwolsman SE, Roovers JWR. 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. doi: 10.1002/nau.23299

**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 Sep;29(9):1249-1257. doi: 10.1007/s00192-018-3644-0.

**Casteleijn FM**, Enklaar RA, El Bouyahyaoui I, Jeffery S, Zwolsman SE, Roovers JWR. How cure rates drive patients' preference for urethral bulking agent or mid-urethral sling surgery as therapy for stress urinary incontinence. Neurourol Urodyn. 2019 Jun;38(5):1384-1391. doi: 10.1002/nau.23997.

**Casteleijn FM**, Kowalik CR, Berends C, Blaganje M, Lasić Pecev M, van der Linden E, Zwolsman SE, Roovers JWR, 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. doi: 10.1002/nau.24417.

Allert M de Vries, **Fenne M Casteleijn**, Jan-Paul W R Roovers, John P F A Heesakkers, Jurgen J Fütterer. Imaging findings of vinyl dimethyl polydimethylsiloxane used as a paraurethral injectable for female stress urinary incontinence. Ther Adv Urol. 2021 Dec5;13:17562872211060909. doi: 10.1177/17562872211060909.

Yani P Latul, **Fenne M Casteleijn**, Sandra E Zwolsman, Jan-Paul W R Roovers. Sexual Function Following Treatment for Stress Urinary Incontinence With Bulk Injection Therapy and Mid-Urethral Sling Surgery. J Sex Med. 2022 Jul;19(7):1116-1123. doi: 10.1016/j.jsxm.2022.03.620.

**Casteleijn FM**, de Vries AM, Tu LM, Heesakkers JPFA, Latul Y, Kowalik CR, van Eijndhoven HWF, van Eekelen R, Roovers JWR. Cost-effectiveness of urethral bulking polydimethylsiloxane-Urolastic® compared with mid-urethral sling surgery for stress urinary incontinence: A two-arm cohort study. BJOG. 2023 May;130(6):674-683. doi: 10.1111/1471-0528.17396

## PHD PORTFOLIO

| Year | ECTs | Specification |
|---|---|---|
| **Courses** | | |
| 2015 | 1,9 | Qualitative health research |
| 2016 | 1,5 | BROK: legislation and organization for clinical researchers |
| 2016 | 0,1 | Endnote |
| 2016 | 1,5 | Scientific writing in English |
| 2017 | 0,6 | Observational clinical Epidemiology: Effects & Effectiveness |
| 2017 | 0,5 | Research datamanagement |
| 2017 | 1,4 | Practical Biostatistics (e-learning) |
| **Seminars, workshops and master classes** | | |
| 2016-2021 | 2,6 | Weekly Research Meeting Research Institute and progress reports |
| 2016-2020 | 1,0 | Urolastic research meetings |
| 2017 | 0,5 | Presentation Journal club Gynaecology and Obstetrics AMC |
| 2017 | 0,5 | Presentation Spinoza lecture AMC |
| **Presentations** | | |
| 2014 | 0,5 | Poster presentation: Patient preferences for Single Incision Midurethral Sling and Transobturator standard midurethral sling tot treatment of stress urinary incontinence in women. European Urogynaecology Assocation (EUGA): Leading Lights, annual meeting, October 2-5, Athens, Greece. |
| 2017 | 0,5 | Poster presentation: The patients' perspective on urethral bulking agents and mid-urethral sling surgery as a primary treatment option for stress urinary incontinence. 47th International continence society (ICS) annual meeting, September 12-15, Florence, Italy |
| 2020 | 0,5 | Oral presentation: Patients' satisfaction and safety of bulk injection therapy Urolastic® for treatment of stress urinary incontinence: a cross-sectional study. 45th International Urogynecological Association (IUGA) annual meeting, August 29 – September 4, virtual, the Netherlands |

**(Inter)national conferences**

| | | |
|---|---|---|
| 2014 | 1,5 | European Urogynaecology Assocation (EUGA): Leading Lights, annual meeting, October 2-5, Athens, Greece. |
| 2016 | 1,3 | 41st International Urogynecological Association (IUGA) annual meeting, August 2-6, Cape Town, South Africa |
| 2016 | 1,3 | 9th European Urogynaecology Assocation (EUGA): Leading Lights annual meeting, 3-5 November 2016, Amsterdam, The Netherlands |
| 2017 | 1,5 | 47th International continence society (ICS) annual meeting, September 12-15, Florence, Italy |
| 2020 | 1,5 | 45th International Urogynecological Association (IUGA) annual meeting, August 29 – September 4, virtual, the Netherlands |

**Supervising**

| | | |
|---|---|---|
| 2016 | 1,0 | Vivian Gerretsen, master thesis |
| 2016 | 1,0 | Suzanne Roskam, master thesis |
| 2016 | 1,0 | Fleur van der Vaart, master thesis |
| 2017 | 1,0 | Roosje Enklaar, master thesis |
| 2017 | 1,0 | Moyra van Nieuwamerongen, bachelor thesis |
| 2017 | 1,0 | Ikram El-Bouyahyaoui, master thesis |
| 2017 | 1,0 | Demi Dorrepaal, master thesis |
| 2017 | 1,0 | Brita Kortz, master thesis |

**Other**

| | | |
|---|---|---|
| 2016 | 1,5 | Grant writing and receiving: ZonMw Open Ronde 2017 programma DoelmatigheidsOnderzoek, oproep Onderzoek naar nieuwe veelbelovende interventies. Cost-effectiveness of a Non-degradable Urethral Bulking Agent as compared to Mid-urethral Sling surgery in women with Stress Urinary Incontinence. Projectnummer 843001710. June 30 2016 |
| **Total** | **30,2** | |

## ABOUT THE AUTHOR

Fenne Casteleijn was born on the 15th of November in 1985 in Utrecht, the Netherlands. After her graduation in 2005 from the secondary school at Bonifatius College Utrecht, she started studying Pharmaceutical Sciences at the Vrije Universiteit in Amsterdam. In 2006 she was accepted to start medical school at the University of Amsterdam. During her study she followed an internship on the Department of Obstetrics and Gynecology at Francis Hospital in Katete, Zambia. It was during her scientific internship about patients preference on different suburethral slings that she met Prof. dr. J.P.W.R Roovers. In 2015 she graduated cum laude from medical school and started working as a resident not in training on the department of Obstetrics and Gynaecology at Spaarne Gasthuis, location Haarlem. Thereafter, she applied for PhD student under the supervision of Prof. dr. J.P.W.R. Roovers at the University of Amsterdam. During her PhD period she worked as a resident not in training on the department of Obstetrics and Gynaecology at the University Medical Centre location AMC. In 2018-2019 she did voluntary work at “Doctors of the World” that offers medical help for people without a valid residence permit or refugees.

In 2020 she started her training for general practitioner at the Leids Universitar Medical Centre in Leiden. She currently works in a primary care health centre as a resident in training for family doctor in The Hague.

She is the fiancé of Maarten van den Berg and lives together with their two sons Seger and Mats in The Hague, the Netherlands.

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