Sling surgery for stress urinary incontinence; the perfect solution?

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Colofon

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General introduction

1

General introduction

Urinary incontinence (UI) is a common condition that affects millions of people worldwide. Although UI is not a fatal condition, it is associated with severe negative effects on various aspects of life and is therefore considered a major burden by most of its sufferers (1-4). Stress urinary incontinence (SUI) is the most observed type of UI and is defined as the loss of urine following a rise in abdominal pressure such as laughing, sneezing and coughing (1). In women, SUI arises from damage to the muscles, nerves, and connective tissue of the pelvic floor due to causes such as childbirth, surgery, radiation and ageing. In men SUI is mostly observed after prostate surgery which, due to an increase in surgical procedures performed, is encountered more frequently in common day urological practice (5-7). Studies in the Western world currently estimate that up to 60% of the female population between 15-64 years suffer from SUI, with a rapid increase in prevalence at ages 70 through 80 (8;9). In males UI has an estimated prevalence that varies from 11% (60 to 64 years of age), to 31% in those aged 65 years or over. The biggest difference between UI in male and female sufferers, is that in males urge urinary incontinence (UUI) accounts for 40% to 80% of the UI, whereas SUI represents the largest part in females (10).

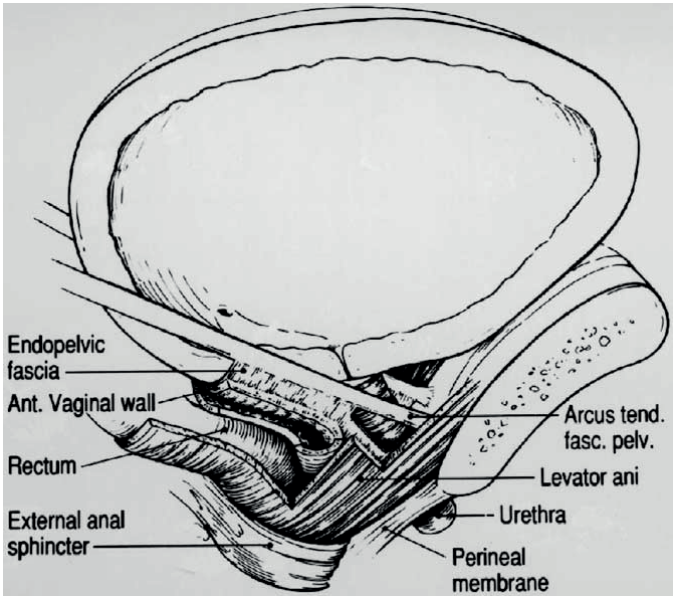
The pathophysiology of SUI in women

Although the concept of maintaining urinary continence (keeping urethral closing pressure higher than bladder pressure) is pretty straight forward, the theories on the pathophysiology of SUI in women have evolved considerably over the past centuries. In 1912, Kelly was the first to publish a clinical description of what we now call SUI (11). In his paper Kelly described an open vesical neck seen with the urethrascope which he subsequently corrected with a surgical procedure that plicated the vesical neck. The 'Kelly plication' became the first routine clinical procedure for the treatment of SUI. During the following decades more and more theories on SUI were presented that focused mainly on anatomical defects, blaming the lack of support of the anterior vaginal wall and subsequent urethral and bladder prolapse (12-16). This one-dimensional vision gradually changed from the 1930's, when theories gradually included the dysfunction of the urethra as possible cofactor in the search for the cause for involuntary leakage of urine (12;15;17). Nowadays these theories have evolved into various complex pathophysiological concepts based on both functional and anatomical mechanisms, that focus on two principal systems; the loss of supportive tissue surrounding the urethra and vesical neck, and dysfunction of the sphincteric system (14;15;18;19).

The following sections will briefly describe these two mechanisms as they are crucial for understanding the basic working mechanisms of the surgical interventions on which this thesis is based.

Loss of urethral support

The urethral support system provides a supportive layer on which the urethra and vesical neck rest and consists of all the structures that surround the urethra. The major components of this system are the anterior vaginal wall, the endopelvic fascia, the arcus tendineus fasciae pelvis and the levator ani muscle.



Lateral view of the components of the urethral support from the article of DeLancey et al. (14)

One of the easiest ways to explain the working mechanism of this supportive system is by describing the 'Hammock Hypothesis', which was proposed in 1994 by DeLancey (18). In this paper he describes the supportive layer (composed of the endopelvic fascia and the anterior vaginal wall) on which the urethra lies as a 'hammock' which gains it structural stability through its lateral attachment to the arcus tendineus fasciae pelvis and levator ani musculature. During an increase in abdominal pressure (e.g. when sneezing or coughing) and the concomitant increase in intravesical pressure, two things happen concurrently that help maintain continence. First the contraction of the levator muscles will tighten the hammock-like supportive layer and elevate the urethra and bladder neck. Simultaneously, the pressure from above compresses the urethra against this hammock, closing its lumen and preventing leakage.

Damage to one or more of the major components of the urethral support system (for instance neuromuscular damage during childbirth), can result in SUI. One of the simplest analogies for this mechanism is to compare the urethra to a garden hose which is being compressed by stepping on it. If the hose would be lying on a noncompliant

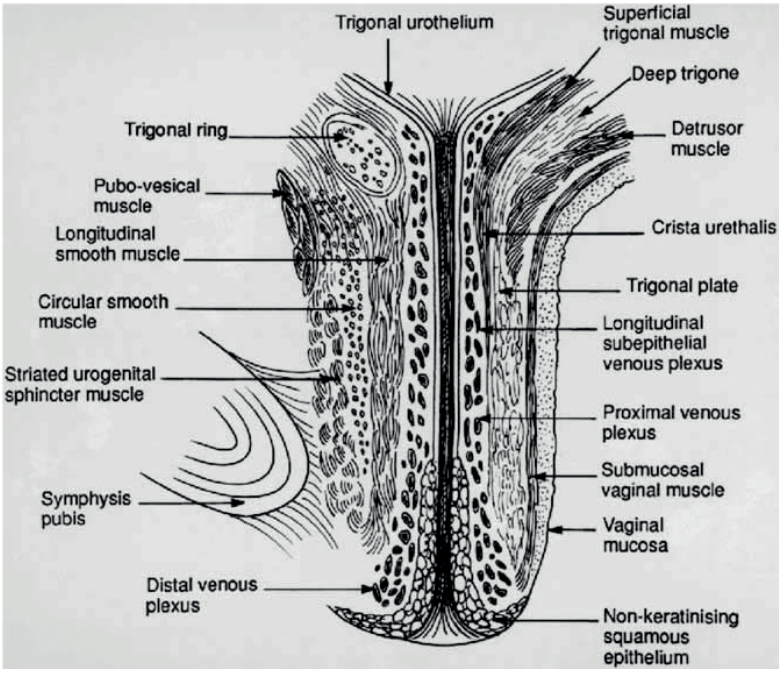
surface (an undamaged urethral support system in this instance), stepping on it would result in closing of the lumen and cessation of the water flow. If the surface would be compliant however (a damaged urethral support system), the hose and surface would simply move downward together when stepping on it, thus resulting in the leakage of water (or urine).

The sphincteric closure system

The second system that is strongly associated with SUI and crucial in understanding the pathophysiology, is the sphincteric closure system or urethral function (14;20;21) . As mentioned earlier, SUI is characterized by the involuntary loss of urine when bladder pressure exceeds the maximum urethral pressure. Urethral pressure is achieved by the sphincteric closure system and should exceed bladder pressure, both at rest and during stress, for urinary continence to occur. The physiologic measure of urethral competence is known as the maximum urethral closing pressure (MUCP). The MUCP is achieved by the collaboration of three main structural components: the striated periurethral muscles (rhabdosphincter), the urethral circular smooth muscles, and the vascular plexus within the submucosa (22).

As the urethra emerges from the bladder wall it is surrounded by a U-shaped loop of striated sphincter muscle. When activated, this loop of muscle will close the lumen of the urethra by constriction. The urethral circular smooth muscle layer can be found in multiple layers of the urethra. The exact role of these layers of smooth muscle still remains to be elucidated, but its circular configuration suggest that it also helps in constricting the urethral lumen when contracted. The vascular submucosal plexus is believed to keep the urethra watertight by forming a vascular cushion and is surrounded by both the striated and circular smooth muscles.

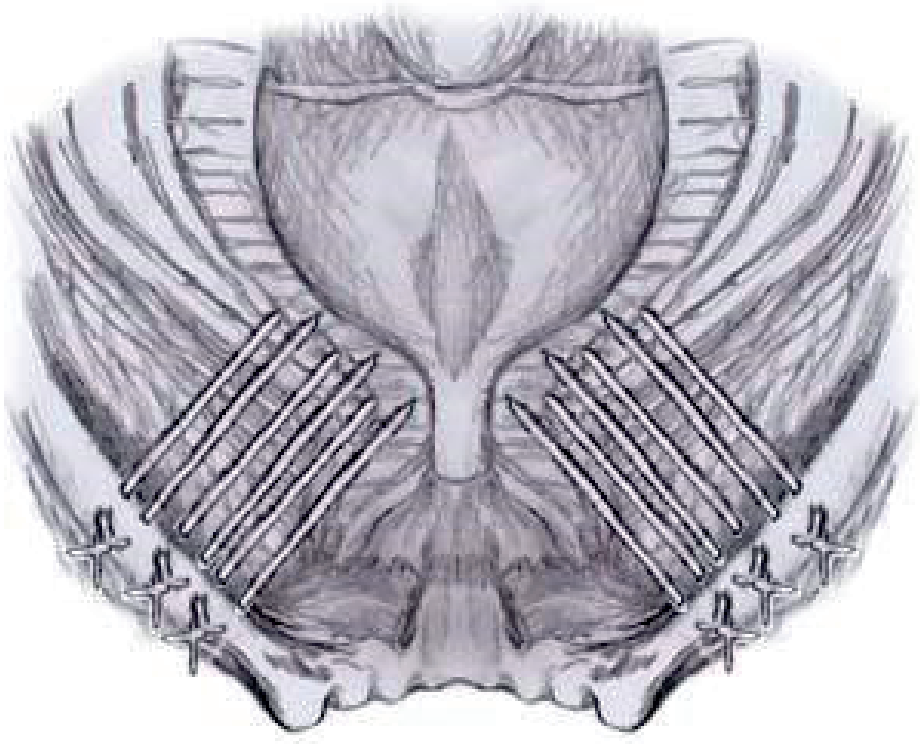
When one (or more) of these three components is damaged, the ability of the sphincteric closure system to adequately react to a sudden increase in abdominal pressure will subsequently be reduced, and could potentially lead to the loss of urine. In incontinent women, the loss of circular smooth muscles and striated muscles are believed to result from both nerve damage (eg. during vaginal childbirth) and age-related deterioration due to hypoestrogenism (24-28). The vascular submucosal plexus is known to weaken in postmenopausal women as well, probably as a result of hormonal changes (25;29-31).



Midsagittal section showing the anatomy of the urethra from an article by Strobehn et al. (23)

A brief history of surgery for SUI in women

Since Kelly introduced his revolutionary technique in 1912, a lot has changed in the surgical treatment of SUI. The most important advancements after the Kelly plication came in 1949 and 1961, when F. Marshall, A. A. Marchetti and K. E. Krantz, and J. C. Burch introduced their methods of an anterior urethropexy and colposuspenion (32;33). The Marshall-Marchetti-Krantz (MMK) and Burch procedures use an open retropubic approach to place non-absorbable stitches in order to suspend and stabilize the urethra. This suspension and stabilization then allows normal pressure transmission during periods of increased intra-abdominal pressure, thus restoring continence. Both the MMK and the Burch procedures reach cure rates of about 80% after an extended period of time. The Burch soon became the 'gold standard' procedure against which other operative managements of SUI were compared (34-36).



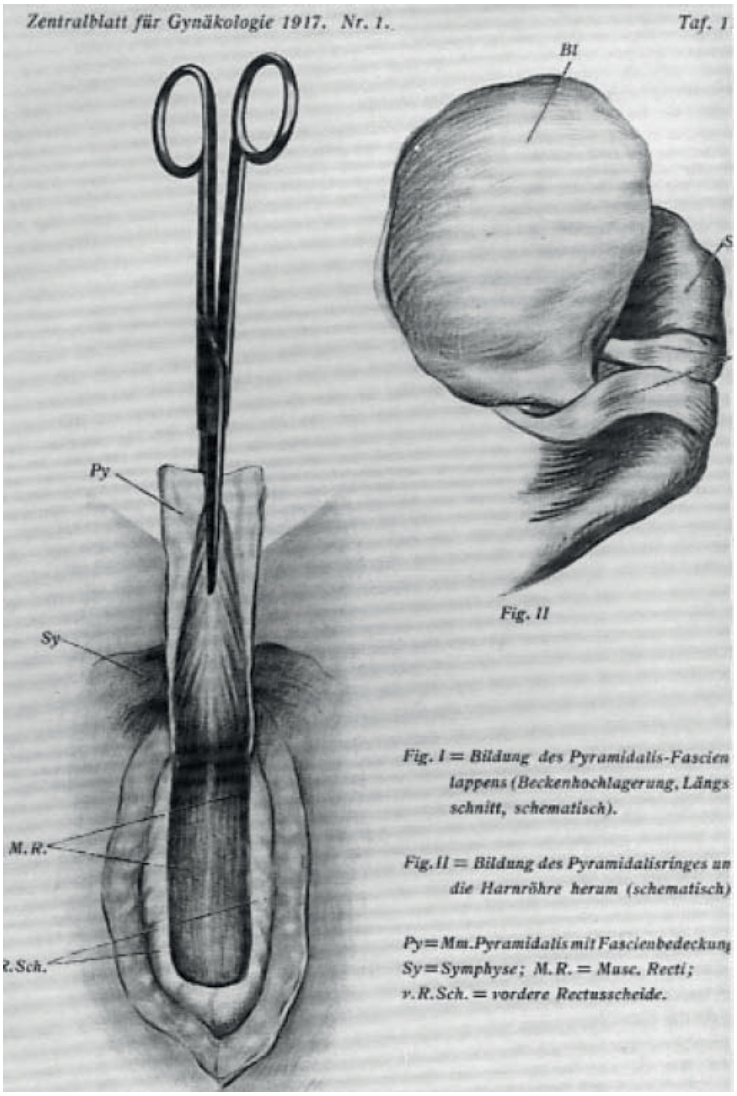
Burch colposuspension (source: emedecine.medscape.com)

Another technique that has to be mentioned in this brief history on the surgical treatment of SUI is the needle suspension. The first needle suspension was introduced in 1959 by A.J. Pereyra as a minimally invasive improvement on the MMK procedure and did not require an open abdominal retropubic dissection (in contrast to the MMK and Burch) (34). The Pereyra needle suspension uses a long needle to thread sutures from the vagina to the anterior abdominal fascia through either a vaginal or trans-abdominal approach. The sutures are placed in the para-urethral tissue on either side of the bladder neck, thereby stabilizing and supporting it. In the following years, the initial procedure was altered and modified several times by others such as Raz, Stamey and Gittes (37-39). For decades the needle suspension was considered one of the treatments of choice for SUI but has nowadays largely fallen out of favor due to its poor long-term results (40).

Sling surgery for SUI

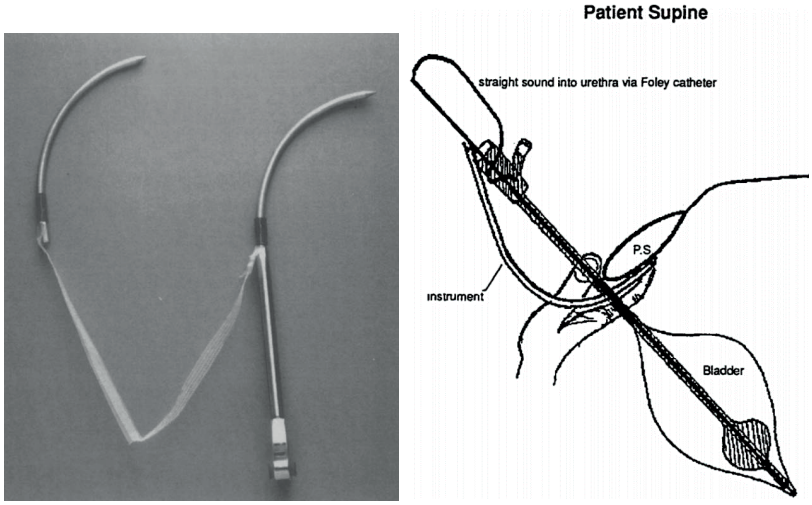
Based on the concept of SUI being caused by the loss of supportive tissue around the urethra (see the section on the pathophysiology of SUI in women), physicians at-

tempted to correct these anatomical abnormalities with the use of pubovaginal slings as early as the 1900's (41-43).



One of the first pubovaginal slings; the retropubic pyramidalis muscle–fascia sling according to Walter Stoeckel (1917) (43)

Throughout the years numerous different techniques and slings, both autologous and synthetic, have been used in an attempt to effectively cure SUI with a wide variation in success rates. This all changed in 1995, when Papa Petros and Ulf Ulmsten described the use of a revolutionary, new, minimally invasive intravaginal sling plasty as a method of restoring the posterior pubourethral ligament. This procedure, which was henceforth known as the IVS, was performed on 50 patients and reached a cure rate of 78% (44). It would, however, be the paper by the same Ulmsten in 1996 that truly rocked the foundation of the treatment for SUI (45). In this paper he presented the results of the modified version of the IVS: the TVT. This modified sling, fully named the Tension-free Vaginal Tape®, is a polypropylene tape that is transvaginally placed in a mid-urethral position using two needles through the cavum Retzii. The TVT creates an artificial tension free hammock-like suspension underneath the urethra, providing the support needed to restore continence during an increase in abdominal pressure. The initial study on the TVT included 75 women with (genuine) stress urinary incontinence and presented a postoperative cure rate of 84% after a follow up of two years. What made the TVT so revolutionary was the fact that it combined impressive cure rates with a minimally invasive surgical technique that could be performed under local anesthesia, little per- and postoperative complications and a huge decrease in operative time. The TVT rapidly gained worldwide popularity due to this unique combination and it soon became (and still is) the gold standard in the surgical treatment of SUI.



Original photo of the TVT and its technique used in the article by Ulmsten in 1996 (45)

Introduction of new slings for the treatment of SUI in women

Following the successful introduction of the TVT, with its relatively simple but hugely effective technique, it did not take long for medical companies (and physicians) to realize the enormous potential of synthetic slings for the use in incontinence surgery in women. Since 1995 there have been dozens of newly marketed synthetic slings and techniques, all claiming to achieve equal, if not better, results in comparison to the original TVT. Nonetheless, peer-reviewed scientific literature, mostly performed after the commercial introduction, identified serious safety and effectiveness concerns on many of these 'revolutionary' new slings and techniques (46-48). Currently, when a new drug is introduced, the (obligatory) research conducted may take up to 12 years and include well over a 100.000 pages of research protocols, presented evidence and test results. It is only after this extensive evaluation that a new pharmaceutical product receives its Food and Drug Administration (FDA) clearance or Conformité Européenne (CE) mark and can be launched for commercial use.

In contrast to the introduction of a new pharmaceutical, a new medical product such as a sling, is cleared for sale in the USA after making assertions to the FDA of "substantial equivalence" under section 510 (k) of the Food, Drug and Cosmetic Act. According to the FDA, substantial equivalence is established with regard to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labelling, biocompatibility, standards and other characteristics, as applicable. In short this act states that any new device should be at least as safe and effective as comparable devices already marketed, without the need of any (published) premarket research. In the European Union a CE mark notification is obtained by approval from an independent notified body and a declaration of conformity. When seeking approval by an independent notified body this is usually done by site audits and an assessment of technical documentation. A declaration of conformity is a statement by the manufacturer that the product meets the requirements of the European directive. As in the USA, this procedure does not require any additional research on either the safety or efficacy of the sling. If the device is permitted, the company receives a clearance to market by the FDA or, in Europe, the CE mark. As most devices are relatively comparable with an established sling such as the TVT, permission is generally granted without major obstacles.

SUI and UI curing surgery in men

Two of the most frequently performed surgical procedures in urology are the radical prostatectomy (RP) and the transurethral resection of the prostate (TURP). Two of the major complications following these surgical procedures are stress urinary incontinence (SUI) and sexual dysfunction (SD) (5;6;49;50).

SUI following a prostatectomy may be caused by either sphincter dysfunction or bladder dysfunction. SUI following a TURP is usually caused by damage to the proximal part of the (rhabdo) sphincter distal to the seminal colliculus (7). The post-RP SUI rates show a wide range throughout literature, but incontinence rates as high as 87% have been reported in the past (51). Despite an evolution in surgical techniques for RP following the introduction of the (robot-assisted) laparoscopic prostatectomy over the past years, recently reported postoperative SUI rates are still between 5% and 48% (52). Incontinence following a TURP is usually estimated around 5% and has a significant impact on the quality of life of its sufferers (4). Initial therapy following SUI after either a RP or TURP consists of lifestyle interventions, scheduled voiding and pelvic floor muscle training. After initial treatment has failed, invasive therapy is often the next option. The current gold standard in the invasive treatment for SUI after prostate surgery is the implantation of an artificial urinary sphincter (AUS). The first, externally worn, urethral cuff was introduced in 1947 by Foley and its subsequent modifications by Kaufman in 1973 eventually led to the first fully internal AUS (53;54). Since then, the AUS has proven itself to be an effective method of curing all types and degrees (mild to severe) of UI in males (including SUI) and success rates vary between 59% and 91.4% in current literature (55-57). The AUS has a serious downside however; surgical revision due to malfunction, erosion or pain is often required and explantation rates can be as high as 36% within 5 years (57-59).

In the search for a less invasive but equally effective technique, the development of synthetic slings for the use in male incontinence surgery has expanded enormously these past years. Parallel to the slings in female SUI, male slings are currently being introduced in a wide variety of shapes, sizes, materials and techniques. In contrast to novel slings in women however, male patients undergoing these new surgical techniques are for the greater part included in cohort studies focusing on the functioning and safety of these devices. Some of these techniques have indeed shown promising results in preliminary studies, but solid (Grade I and II) evidence is still lacking and the AUS remains the gold standard up to the present day (57).

Incontinence surgery and SD

In female patients, one logically hopes that incontinence curing surgery improves the sexual function by eliminating the disabling effects of the loss of urine. If one conducted a literature search on this subject however, you would find that this theory has in fact not been confirmed in current literature (57-67).

One logical explanation for this phenomenon would be the neurovascular damage or anatomical changes caused by the surgery or implant itself (68;69). However, despite millions of female slings having been implanted worldwide, only a limited number of

studies actually address the neurological and vascular risks and provide detailed information on the anatomical relationship between slings and the pelvic nerves.
Although the link between UI and SD in women is a fairly straightforward one, this is a much more complex issue in male patients. As mentioned earlier, two of the most frequently encountered functional complications following prostate surgery are erectile dysfunction and SUI (6;49;50). If a patient suffers from SUI after prostate surgery and finds himself in the need of invasive therapy (e.g. AUS or male sling), it is a complicated task to establish the actual effects (improvement or worsening) of the incontinence surgery on sexual functioning. Nevertheless, a male sling could just as easily cause neurovascular damage and thereby (further) impair sexual function.

Outline of this thesis

The aim of this thesis is to evaluate the efficacy and safety of slings in urological and uro-gynecological (male and female) practice. This thesis consists of eleven chapters and is comprised of clinical data, anatomical studies and reviews on available literature on both male and female slings. The main question of this thesis is whether slings, old and new, for either male and female, can live up to the expectations of both patients and physicians by being both safe and effective in curing urinary incontinence. Secondly, the question is raised whether sling surgery is anatomically safe with regard to those nervous systems which are essential for the sexual function or may actually be responsible for iatrogenic neurological damage during placement.
To solve this issue, it must first be assessed how a new sling is actually introduced on the commercial market and which evidence is used and presented in the process by its inventors and manufacturers. In order to achieve this objective, the pre-market research performed on new mid-urethral slings for curing stress urinary incontinence in women was evaluated and the results are presented in **chapter two**.
The MiniArc® is one of the more recently introduced 'mono incision minislings', that aims to treat SUI with a less invasive, but equally effective sling technique in comparison to the original TVT. **Chapter three** describes the clinical results of the MiniArc sling in a cohort of women after one year.
This thesis continues in **chapter four** with a study that describes the efficacy and safety of mid-urethral slings in a non-selected population of women in the specialized pelvic floor center of a Dutch teaching hospital.
Up to present there is no consensus on the correct treatment of late complications (erosion and/or displacement) following sling surgery in women. **Chapter five** describes the results of a surgical procedure that uses a collagen sling implant following partial

removal of a synthetic sling due to erosion and/or displacement in a tertiary referral center.

As mentioned earlier, one of the most common complications after a TURP is SUI. Little is currently known on the efficacy of sling surgery in this specific group of patients. **Chapter six** describes the effects of the Virtue® male sling for treating incontinence following a TURP. Moreover an overview of the available literature on sling surgery following incontinence in TURP patients is presented.

Neuro-anatomical studies on incontinence curing slings are relatively rare and are seldom found in current literature. In order to extend this knowledge we conducted two studies on the course of these slings in the male and female pelvis. In **chapter seven** and **eight** the possible side effects of sling surgery in both sexes (Tension Free Vaginal Tape®, Tension free Vaginal Tape-Obturator® and AdVance® male sling) are evaluated from a neuro-anatomical point of view. These chapters focus on the actual course of these slings in both the male and female pelvis and describe them in relation to the pelvic nerves that are vital for the sexual function.

Chapter nine provides an English summary (abstracts) and in **chapter ten** the main findings and implications of this thesis on future practice and research are discussed. In **chapter eleven** the Dutch summary of the thesis is provided.

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The introduction of mid-urethral slings: an evaluation of literature

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Introduction

Over the last two decades, synthetic mid-urethral slings (MUS) have changed urogynecological surgery for stress urinary incontinence (SUI) in women. The tension-free vaginal tape (TVT; Women's Health & Urology, Ethicon, Johnson & Johnson) was introduced by Ulmsten et al. in 1996 (1). With a reported 16-year success rate of 70–90% and a low risk of complications, the technique has proven to be effective and safe over the years (2;3). The principle of the TVT is based on restoring the anatomy and function of the mid-urethra, resulting in the restoration of the patients' continence using minor surgery. The TVT therefore became the cornerstone of surgical treatment for SUI.

Soon after the introduction of the TVT other MUS devices started reaching the market. Over the last decade, numerous MUS devices have been introduced, and although these products claimed to have sufficient similarity to the gold standard TVT, nowhere near all the devices were able to achieve comparable results (2–5). So far, more than 2 million women worldwide have had surgery using MUS. With an ageing population and the increasing availability of healthcare worldwide, this number is sure to increase over the coming years.

In order to provide optimal care for patients, new pharmaceutical products are introduced after extensive, strictly reviewed, and standardized research to ensure safety and efficacy. It is only after intensive evaluation that a new product receives its Food and Drug Administration (FDA) clearance or Conformité Européenne (CE) mark and can be launched for commercial use. In the sling industry, however, companies can introduce a new device without comparative studies. That this method of introduction is far from optimal and can even result in unsafe situations for patients is illustrated by the Mentor ObTape™, which was introduced in 2003 and caused vaginal erosion and obturator abscesses in an unacceptably large proportion of patients (4).

Over the past few years a global discussion has flared up about the regulation of the introduction of new medical devices, such as slings, onto the market. This worldwide problem had already been recognized and extensively analysed in an "editorial" in 2011 by Abrams et al. in the journal European Urology (6). Although this paper very clearly described the problems with the introduction of vaginal slings and proposed well-grounded recommendations, so far, no action has been undertaken by the official bodies responsible.

The first part of this study provides an overview of the degree and reliability of evidence used by the manufacturers before the introduction of MUS onto the commercial market by reviewing pre-introduction data. The second part presents minimum standards for marketed slings by evaluating recent suggestions regarding the introduction of urogynecological meshes devised in an IUGA round-the-table session (7;8).

Materials and methods

The aim was to review and evaluate the research on MUS that was conducted before the launch of a particular sling onto the commercial market. A search for literature was conducted using PubMed and commercial internet search engines (Google ™, Yahoo™) to attempt to identify most types of MUS introduced by the industry over the last decade. Slings were listed and a literature search was performed using MESH terms: "stress urinary incontinence," "mid urethral sling," and brand and/or company name of the sling to identify any pre-launch data. "Related articles" were used to expand the search. Moreover, manufacturers were contacted by email, mail, and phone to provide data used before the introduction of the sling onto the commercial market. Requested data included articles published in either peer-reviewed or non peer-reviewed journals, online data, manuscripts, presentations, brochures, personal communications, and unpublished research. Companies received multiple reminders by mail, by email, and by phone. At the end of the established 6-month deadline, all data received were structured and divided into multiple categories. In the discussion an "experts round the table" discussion by urogynecologists, specializing in SUI, was used to obtain expert views. The design of this study does not include medical research involving human subjects; therefore, no approval of the Medical Ethics Committee was needed.

Results

Forty-one sling devices introduced between 1996 and 2012 were identified (Table 1). Of these 41 slings, 10 were described in a total of 20 studies with sample sizes varying from 10 to 368. The studies included comprised a total of 1,633 patients. Two randomized controlled trials were identified, one of which was published (9); all other studies were non-randomized case series. A total of 6 studies were conducted in a multicenter setting. Thirteen of the studies described were published in peer reviewed journals; the other studies were either unpublished or not publicly available (Tables 2, 3) (1;9-19). Two studies were orally presented at an international conference. The number of articles per sling varied from one to four (Tables 2, 3).

Table 1 Type and manufacturer of MUS

Sling	Technique	Year of approval by FDA/CE	Manufacturer	Company Headquarters
Monarc	Trans-obturator	2002	AMS	Minnetonka Minnesota, USA
Sparc	Retropubic	2004	AMS	"
Miniarc	Single incision (TO)	2007	AMS	"
Uretex	Trans-obturator	2004	Bard	Murray Hill, New Jersey, USA
Pelvilace	Trans-obturator	2004	Bard	"
Align	Retropubic	2010	Bard	"
Ajust	Single incision (TO)	2012	Bard	"
Lynx	Retropubic	2004	Boston Scientific	Natick, Massachusetts, USA
Protegen^	Urethropexy	1996	Boston Scientific	"
Prefyx	Prepubic	2007	Boston Scientific	"
Advantage	Retropubic	2007	Boston Scientific	"
Solyx	Single incision (TO)	2008	Boston Scientific	"
Obtryx	Trans-obturator	2012	Boston Scientific	"
Retropubic I-stop	Retropubic	2005	CL Medical	Winchester , Massachusetts, USA
Trans-obturator I-stop	Trans-obturator	2006	CL Medical	"
Aris	Trans-obturator	2005	Coloplast	Humlebæk, Danmark, EU
Supris	Retropubic	2011	Coloplast	"
T-sling	Trans-obturator	2012	Coloplast	"
Minitape*	Single incision (TO)	2008	Mpathy Medical	-
Omnisure*	Trans-obturator	2009	Mpathy Medical	-
Obtape**^	Trans-obturator	2003	Mentor Medical	-
Sabre**	Trans-obturator	2003	Mentor Medical	-
Uratape**^	Trans-obturator	‡ 2000	Mentor Medical	-
Biodesign Surgisis	Retropubic	2002	Cook Medical	Bloomingdale, Indiana, USA
Intramesh Lift	RP/TO	‡‡ 2012	Cousin Biotech	Wervicq-Sud, France, EU
IVS	Retropubic	2001	Covidien/Tyco	Dublin, Ireland, EU
EmeraldPlus	Single incision	‡‡ 2006	Gallini	Mantova, Italy, EU
T-sling	RP/TO	2002	Herniamesh	Chivasso, Italy, EU
TVT	Retropubic	1996	Johnson & Johnson	New Brunswick, New Jersey, USA
TVT-Obturator	Trans-obturator	2003	Johnson & Johnson	"

Table 1(continued) Type and manufacturer of MUS

Sling	Technique	Year of approval by FDA/CE	Manufacturer	Company Headquarters
TVT-Secur^^	Single incision (TO, RP)	2005	Johnson & Johnson	"
TVT-Abbrevo	Trans-obturator	2010	Johnson & Johnson	"
Remeex	Retropubic	2004	Neomedic	Terrassa, Barcelona, Spain, EU
Needleless TOT	Single incision (TO)	2006	Neomedic	"
Safyre	RP/TO	2002	Promedon	Cordoba, Argentina
Ophira	Single incision (TO)	2012	Promedon	"
Minisling	Single incision (TO)	2007	Prosurg	San Jose, California, USA
Serasis	RP/TO	‡‡ 2007	Serag Wiessner	Naila, Germany, EU
Swing-band	Trans-obturator	‡‡ 2006	Texhitec	St. Pons de Thomières, France, EU
Just Swing	Single incision (TO)	‡‡ 2009	Texhitec	"
TFS	Single incision (TO)	2005	TFS Surgical	Allenby Gardens, Australia

TO: transobturator, RP: Retropubic
^ Withdrawn from market due to high complication rate
^^ Withdrawn from market
* Previously produced by Mpathy Medical, acquired by Coloplast in 2010
** Previously produced by Urology division of Mentor Medical, acquired by Coloplast in 2006
‡ Introduced on European market only, withdrawn due to disappointing results
‡‡ Introduced on European market only

Cure rates found ranged from 78 to 92%. Three studies did not mention any success rates. Reported follow-up ranged from 1 to 36 months, with a mean of 11 months. Complication rates showed a large variation throughout the studies (0-22.1%). These complications included bladder injuries, urinary retention, vaginal erosion, vaginal abscesses, voiding difficulties, and de novo urge incontinence. None of the articles used expressed negative opinions or made any objection about the particular product and its introduction onto the commercial market.

Table 2 Companies and response

Company	Number of slings†	Response*	Data received^	Number of slings with data^^	Data in peer reviewed journal
AMS	3	Yes	Yes	1	YES
BARD	4	Yes	No	0	-
Boston scientific	6	Yes	No	0	-
CL medical	2	No	No	0	-
Coloplast**	8	Yes	Yes	1	NO
Cook Medical	1	Yes	No	0	-
Cousin Biotech	1	Yes	Yes	1	YES
Covidien	1	No	No	0	-
Gallini	1	No	No	0	-
Herniamesh	1	No	No	0	-
J&J	4	Yes	Yes	3	YES
Neomedic	2	Yes	Yes	2	YES
Promedon/ pelvitec	2	Yes	Yes	2	YES
Prosurg	1	No	No	0	-
Serag Wiessner	1	No	No	0	-
Texhitec	2	Yes	No	0	-
TFS Surgical	1	No	No	0	-

† Included in this research

* Response received by either mail, phone or email.

** Including tapes by Mpathy Medical, acquired by Coloplast in 2010, and Mentor Medical, Urology division acquired by Coloplast in 2006

^ Data included articles , papers published in either peer-reviewed or non peer reviewed journals, presentations, brochures, and unpublished research. Answer YES/NO

^^ Number of slings by the different companies examined in this paper

The results of one animal study and two cadaver studies were presented. The animal study included 9 rabbits and showed the tissue response up to 3 months after mesh implantation (study by BIOMATECH, October 2004 on the ARIS sling by Coloplast, unpublished). The cadaver studies primarily looked at the trans-obturator technique and both studies included 10 cadavers (12;16).

Table 3 Data on slings

Company	Sling	Nr. of studies	Patients included	Study design	Animal/ cadaver study	Published in peer reviewed journal*
AMS	SPARC	1 [9]	104	Case series	No	Yes (1)
Coloplast	Aris	2	368	Case series	Animal	No
Cousin biotech	LIFT	2	165	1. RCT 2. Case series	No	Yes (1)**
J&J	TVT	2 [1,16]	256	Case series	No	Yes (2)
J&J	TVT-O	3 [8, 14, 17]	170	Case series	Cadaver	Yes (3)
J&J	TVT-Abbrevo	2 [7,10]	185	1. RCT 2. Case series	Cadaver	Yes (2)
Neomedic	Remeex	4 [15]	69	Case series	No	Yes (1)
Neomedic	Needleless TO	1	56	Case series	No	No
Promedon	Safyre	2 [12,13]	240	Case series	No	Yes (2)
Promedon	Ophira	1 [11]	20	Case series	No	Yes (1)

* Published in a peer reviewed journal: YES/NO (number of publications)
** Published in the Austrian specialist journal ***'Geburtshilfe und Frauenheilkunde'***, volume 67, September 2006, not found on PubMed but available online.

The 41 MUS identified were produced by a total of 19 different companies, two of which have been acquired by a third company in the past decade (Table 1). Seven companies never responded to recurrent emails, phone calls or other means of attempted contact. Information was received on 10 MUS; leaving the remaining 31 slings (76%) without comparative pre-launch data.

Discussion

After its introduction in 1996, multiple companies modified or attempted to recreate the original TVT in order to claim a spot in the growing MUS market. Over the years, dozens of new slings, with multiple new techniques and different materials, have been introduced, but not all of these MUS achieved satisfactory results compared with the gold standard TVT.
A new medical product is cleared for sale after making assertions to the FDA of "substantial equivalence" under Section 510(k) of the Food, Drug, and Cosmetic Act. The FDA states on its website that substantial equivalence is established with regard to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labelling, biocompatibility,

standards, and other characteristics, as applicable. In short, this act states that any new device should be at least as safe and effective as comparable devices already marketed. In the European Union, a CE mark notification is obtained by approval from an independent notified body and a declaration of conformity. When seeking approval by an independent notified body this is usually done by site audits and assessment of technical documentation. A declaration of conformity is a statement by the manufacturer that the product meets the requirements of the European directive. If the device is permitted, the company receives a clearance to market by the FDA or, in Europe, the CE mark. As most devices are relatively comparable with existing slings, permission is generally granted without major obstacles. The new implant should then participate in a post-clearance surveillance to validate its rightful niche in the market.

Regarding the MUS that were described in this study, results show a lack of adequate pre-launch data as well as a defect in the accessibility of follow-up data. This was further illustrated by the fact that only 13 studies were actually published in peer-reviewed journals (Tables 2, 3). Eleven out of 17 companies (65%) did or could not provide any information, which makes validating any statement or conclusion difficult. The high percentage of nonresponses after multiple reminders enhances the supposition that these companies may not have the requested data at their disposal or were not willing to cooperate in sharing information. This study is aware of the difficult, grey area that this suggestion may lead to. However, realizing that sling surgery is so frequently performed and that it has such a great impact on quality of life, data should always be easily accessible (20).

In the process of identifying slings for this study the authors at some point had to limit the research. Inevitably, some slings and companies were not mentioned in the paper. To include all slings introduced onto the commercial market over the past few years would of course be the ultimate goal, but proved to be impossible. This limitation had nothing to do with either inclusion criteria or study restriction, but rather the identification of the many individual slings. Moreover, the aim of this project was not to include all slings up to the present day, but to place emphasis on the lack of pre-launch data in general.

This paper illustrates that company databases are often poorly maintained, not validated, highly variable, and may sometimes be non-existent. Keeping this in mind, the concept of "informed consent" is put into a different perspective altogether. How can one clarify whether a newly introduced sling is both safe and effective, without reliable information being provided to both patients and physicians? With the increase in sling surgery worldwide and new products being developed each year, this is a serious and potentially dangerous issue. Furthermore, physicians worldwide should be more reserved when using new marketed devices. Even though it is legal for a physician to implant a new medical device such as MUS, clinicians and their professional organisa-

tions should only choose those devices that have adequate clinical data to support their efficacy and safety.
A parallel to this dilemma can be found in the use of mesh material in vaginal prolapse surgery. An International Urogynecological Association (IUGA) round table conference in 2012 resulted in a paper addressing similar issues (7;8). The paper states that a standard, before the launch and marketing of a new mesh, should be demanded and guarded by the FDA. The group suggested the following four steps to be taken before the introduction of a new surgical device to achieve this:

1. Comprehensive and exact data on the physical properties of the product.
2. Data on the biological properties of the product following implantation from high-quality animal studies.
3. Anatomical studies on cadavers.
4. A well-constructed and documented cohort study

These four obligatory points should then be followed by compulsory registration of the first 1,000 consecutive patients. The registration should not be liable to any bias and therefore not sponsored by companies involved. Furthermore, the first patients should be operated on by a selected group of specialists who are known experts in this area. As mentioned in the introduction, this matter was also discussed in detail by Abrams et al. in 2011, and similar recommendations were suggested (6).
Finally, we propose that in the future full disclosure of data for either FDA clearance or CE notification should be mandatory for all manufacturers of slings in order to ensure complete openness. These submissions should then be analysed by the surgical committee and published in order to encourage clinicians to judge the scientific merit on which the CE mark or FDA clearance was awarded. The combination of these guidelines should ultimately ensure that in the near future all new slings fulfil their obligations of being both safe for patients and likely to produce a significant improvement in incontinence and quality of life.

Conclusion

Often, no reliable pre-launch data is available or presentable to scientifically prove the performance of new MUS. The FDA and European authorities should undertake immediate action by introducing strict rules, comparable with the suggestions made for meshes in vaginal prolapse surgery, before the launch of new MUS.

Addendum

On 29 April 2014 the FDA released the following press announcement:
The U.S. Food and Drug Administration today issued two proposed orders to address the health risks associated with surgical mesh used for transvaginal repair of pelvic organ prolapse (POP). If finalized, the orders would reclassify surgical mesh for transvaginal POP from a moderate-risk device (class II) to a high-risk device (class III) and require manufacturers to submit a premarket approval (PMA) application for the agency to evaluate safety and effectiveness. Although these two proposals do not include the MUS addressed in this study, the surgical mesh used for transvaginal POP repair is essentially the same material (polypropylene mesh) that is used for most MUS. These recent developments only further amplify our call for immediate action by the FDA and European authorities.

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Erratum to: The introduction of mid-urethral slings: an evaluation of literature

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Erratum

The idea for this study originated in 2012 and aimed to check the availability of company databases on mid-urethral slings. Due to the lack of response and data provided by the involved companies, we decided to perform an additional literature search via PubMed to identify available pre-launch data. In this secondary search the FDA or EU date of approval (whichever was earlier) was used as introduction date. The final results of this search were sent to every company involved for verification. Since the publication of our paper however, relevant information has become available on two slings of which we stated that no pre-launch data was available; the TFS and the I-Stop.

The TFS is produced by TFS Surgical (Allenby Gardens, Australia) and received its FDA approval in May 2005 based on a 510 k declaration of substantial equivalence. Following the publication of our article, information was received that the TFS was in fact under review for 5 years (2004–2009) and not commercialized on the date that the FDA approval suggested. During this period the TFS was deliberately withheld from the from the commercial market and multiple studies were conducted and published in various peer-reviewed magazines (1-5).

The second sling, the I-Stop by CL-medical (Sainte-Foy-lès-Lyon, France), was CE-approved during the last quarter of 2002 after a pre-launch case series of 50 patients (not published). Upon approval, the tape had a targeted launch with a limited number of surgeons willing to participate in the clinical evaluation of the sling. The clinical evaluation was then presented as a poster at the National Congress of the French Association of Urology (AFU) in November 2003 and published as an article in the French magazine 'Endomag' in June 2004 (both not available on Pubmed). The first paper available on Pubmed was published in September 2004 in the journal European Urology (6).

Summarizing, the I-Stop was commercially available on the European market from the last quarter of 2002 to November 2003, without any available pre-launch data. However, during this first year the company did restrict the export of the sling to a limited number of specialists.

With this relevant new data available, table 3 of our article is incomplete. Although we feel that companies should provide an insight into their databases upon request, we realize that by stating a systematic review was performed, we, and not the companies involved, are ultimately responsible for data collection. We therefore apologize for these errors and any issues arising from them. Nonetheless, the conclusion of our article remains unchanged: mid-urethral slings are most often introduced without any scientifically proven basis or pre-launch research.

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The MiniArc sling for female stress urinary incontinence: clinical results after 1-year follow-up

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3

Introduction

It is estimated that urinary incontinence (UI) affects 10-40% of the female population aged 15-64 years and has an even higher incidence after 65 years of age (1-3). UI is defined as the uncontrolled and involuntary leakage of urine (4) and is associated with a reduction in quality of life (QoL) for women of all ages (1-3). To assess this reduction, QoL questionnaires are commonly used and focus on the consequences of urinary incontinence (5-9). Stress urinary incontinence (SUI) is described as urinary incontinence following increase of abdominal pressure as in sneezing or coughing and is due to a weakening of the muscles and connective tissue of the pelvic floor.

The wide acceptance of surgery with mid-urethral slings (MUS) as intervention for SUI is due to the effectiveness, rapidity, and minimal invasiveness of the techniques so far. After the first-generation (the tension-free vaginal tape, TVT) and second-generation (the trans-obturator tape, TOT, and the tension-free vaginal tape–obturator, TVT-O) tapes, the industry developed third-generation vaginal tapes like the MiniArc (introduced in 2007 by American Medical Systems) and TVT-Secur (introduced in 2006 by Women's Health & Urology, Ethicon, Johnson & Johnson). The TVT, TVT-O, and the TOT all show cure rates ranging from 84 to 100% after a minimum follow-up of 1 year (10).

The MiniArc uses self-fixating tips and is performed with a single incision in the anterior vaginal wall. With this design, the procedure aims to accomplish minimal tissue damage by lowering the number of incisions from three to one. Also, needle penetration of the obturator foramen or the retropubic space is avoided, thereby minimizing tissue and (potential) organ damage.

Studies of the MiniArc (11-18) show a variance in success rate (range, 69.1-91.4%), after a minimum follow-up of 1 year. Although these studies all assess the cure rate of the MiniArc, only the articles of De Ridder et al. and Pickens et al. (11;18) discuss the impact on everyday functioning and QoL.

It is important to mention that no restrictions were made regarding the study population on the base of severity of SUI, age, BMI, etc. The aim of this study is to perform a 1-year postoperative evaluation of the treatment of SUI using the MiniArc sling with a focus on the efficacy, quality of life, and daily functioning.

Material and methods

A prospective study was performed at the Department of Gynecology of the Flevo Hospital, Almere. In this hospital, 77 primary interventions with the MiniArc were performed by one gynecologist (IMC) from March 2008 to November 2009.

The patient population consisted of women aged 29-82 years who all had clinically established predominant SUI. If a patient was suspected of having urge incontinence due to detrusor overactivity, full urodynamics were performed. In the case of identified detrusor instability, the patient was subsequently excluded from the study. Patients were asked to complete questionnaires preoperatively and 1 year postoperatively.
Inclusion criteria were predominant SUI and a minimum follow-up of 1 year post-surgery. Exclusion criteria were predominant urge incontinence and previous surgery for SUI. It is important to mention that the tape was positioned against the urethra without compression, but the overall placement of the MiniArc was tighter than the traditional MUS. This study was approved by the medical ethics review board of the Flevo Hospital, Almere.

Outcome

Failure of the procedure was defined as persistent SUI, stated by the patient in the questionnaire as loss of urine upon exertion, coughing, or sneezing. Patients not reporting any amount of leakage were considered cured. A post voidal residual volume of 150 ml was considered as the maximum acceptable and treated with Ubretid (5 mg/day) and/or (self) catheterization.

Questionnaire

The questionnaire used has been validated by the Dutch Association for Obstetrics and Gynecology in cooperation with the Dutch Association of Urology to evaluate the impact of urinary incontinence. The questionnaire consists of 47 multiple choice questions and is divided in five sections that evaluate physical condition (health status), micturition status, defecation status, coping of the patient (emotional status), and sexual functioning.
The first part consists of the 5-Dimensional EuroQol instrument (EQ-5D) (19). The EQ-5D is specifically designed to evaluate five different subcategories of the patient's current physical condition (mobility, self-care, daily activities, pain/complaints, mood) and is scored from 1 (no complaints) to 3 (serious complaints). The first part also includes a Visual Analog Scale (VAS), as well as a QOL scale to evaluate the overall health status of the patients.
The next parts evaluate the micturition status using the Urogenital Distress Inventory (UDI) (7), the coping behaviour of the patients using the Incontinence Impact Questionnaire (IIQ) (7), and the defecation status using the Defecation Distress Inventory (DDI) (20). The final part assesses sexual functioning with sections of the Pelvic Organ Prolapse/ Urinary Incontinence Sexual Questionnaire-SF (PIS-Q short form, limited to five questions (21)). The IIQ and UDI were scored using the different domains as described by van der Vaart et al. (9).

The postoperative questionnaire was identical to the preoperative questionnaire except for the first question which assessed the improvement/deterioration post-surgery with the Patient Global Impression of Improvement (PGI-I) (22).

Statistical analysis

Results of both pre- and postoperative questionnaires were scored, and for the UDI, IIQ, and DDI, outcomes were converted to a scale ranging from 0 to 100 (higher= negative). Statistics were performed in SPSS release 17 (SPSS Inc., Chicago, IL, USA). P values <0.05 were considered statistically significant. For multiple comparisons, a Bonferroni correction was conducted after the paired samples *t*-test.

Results

All patients screened for SUI and eligible for surgery with the MiniArc were asked to participate in our study and complete the preoperative questionnaires. Of the operated patients, 77 filled in the preoperative questionnaire and were thus eligible to be included in this study. Clinical characteristics of this patient group are described in Table 1.

Table 1 Clinical characteristics of patients treated with the MiniArc, n=77

Age	52.1±12.6 (range, 29–80)
BMI	28.2±6.1 (range, 17, 63–50, 43)
Parity	2.3±0.9 (range, 1–6)
None	4 (5%)
1–3	68 (88%)
4, >4	5 (7%)
Education	3.4±1.7

Values are given as mean ± SD or percentage. Education rated from 1 (primary school) to 7 (university degree). BMI Body mass index in kilograms per square meter

After 1 year, these 77 patients were sent a copy of the postoperative questionnaire of which 57 were returned (74%). No differences were found in baseline characteristics between responders and non-responders. Of the 77 patients who had primary surgery with the MiniArc, 10 (13%) were anesthetized locally and 67 (87%) had general anaesthesia.

Complications were seen in 6 of 77 patients (8%) and resulted in one cleaving of the MiniArc due to deteriorating urge incontinence. Other complications were dehiscence of the wound (one patient) and a large residue (two patients, 300-600 ml; two patients,

150-300 ml). At the 6 week check, all patients had normal emptying of their bladder. Further investigation showed that the dehiscence was due to a post-surgery hematoma and did not cause any problems after the first week. Success and complications over time are visualized in Table 2.

Table 2 Success and complication rate through time, n=77

	Complications	Success rate[a]	Response[b]
First quartile	2	41.2% (7/17)	17/19=89%
Second quartile	2	50.0% (6/12)	12/19=63%
Third quartile	2	42.9% (6/14)	14/19=74%
Fourth quartile	0	42.9% (6/14)	14/20=70%
Total	6	Mean, 44.0 % (25/57)	Total, 57 patients

Patients divided in quartiles (77/4=19 patients per quartile, 20 in the fourth), chronological order. a: Patient not experiencing any amount of leakage 1 year after surgery, b: Response after 1 year

One-year post-surgery, 44% of the patients stated to be completely continent (Table 3). The patient's subjective satisfaction was scored ranging from "very much better" to "very much worse," using the PGI-I. After 1 year, 68% of the patients rated their current situation as either being "very much better" or "much better." The other 32% stated little improvement or even deterioration of their SUI in comparison to their preoperative status (Table 3).

Table 3 PGI-I, 1 year post-surgery

Very much better	16 (D=13, 3=ND)	(28%)
Much better	23 (D=11, ND=12)	(40%)
A little better	10 (D=1, ND=9)	(17.5%)
No difference	6 (D=0, ND=6)	(10.5%)
A little worse	0	
Much worse	1 (D=0, ND=1)	(2%)
Very much worse	1 (D=0, ND=1)	(2%)
Total	57	
Dry (success)	25 (44%)	
Not dry (failure)	32 (56%)	

Values are given as mean ± SD D dry, ND not dry

Preoperatively the overall QoL mean score was 4.6 with a standard deviation of 0.9. One year after surgery, the QoL did not differ from pre-surgery. The VAS did also not differ significantly1 year after surgery.

The EQ-5D score did not show a significant difference in comparison to the pre-operational status. The part of the questionnaire concerning the micturition status was scored using the UDI (five subcategories). After 1 year, all five subcategories showed an improvement (Table 4).

Table 4 Comparison of pre- and post-operational scores of patients treated with the MiniArc,

	Pre-surgery n=77	1-year, n=57	p value[b]
QoL scale [1–6]	4.6±0.9	4.9±1.0	ns
EQ-5D	0.82±0.19	0.86±0.19	ns
VAS	73.8±17.2	77.3±13.3	ns
Incontinence-related distress (UDI)			
Discomfort/pain	26.6±23.9	13.2±20.1	0.009[a]
Urinary incontinence	58.9±24.1	23.4±25.0	0.000[a]
Overactive bladder	30.7±24.6	13.7±18.7	0.000[a]
Obstructive micturition	26.2±24.8	17.0±23.3	0.024[a]
Genital prolapse	8.4±15.9	3.8±10.0	0.000[a]
Impact on everyday functioning (IIQ)			
Mobility	50.7±18.9	40.0±18.4	0.003[a]
Emotional	49.9±18.3	37.1±14.7	0.000[a]
Physical	40.2±16.1	32.6±12.6	ns
Social	34.3±13.2	29.6±10.7	ns
Embarrassment	53.0±21.6	41.0±17.9	0.006[a]
Defecation disorders (DDI)			
Constipation	11.2±19.8	9.4±15.8	ns
Painful defecation	9.3±18.0	7.3±15.8	ns
Fecal incontinence	7.1±16.8	7.6±16.4	ns
Flatus incontinence	18.6±25.7	23.4±26.0	ns

Values are given as mean ± SD. The p values were Bonferroni corrected. Scale from 1 (no complaints) to 100 (a lot of complaints). Preoperative compared to 1-year postoperative (n=57). QoL: Quality of life from 1 (very bad) to 6 (excellent), VAS: Visual Analog Scale (1–100), EQ-5D EuroQol-5 Dimensions, ns: not significant a: P value <0.05 was considered statistically significant, b: Paired-samples *t*-test, UDI, IIQ, and DDI

The final part of the questionnaire discussed the distress caused by the incontinence and the impact on everyday functioning using the IIQ (five subcategories). Three out of the five items were significantly improved after 1 year, indicating a decrease in distress caused by SUI. The DDI, as expected, showed no differences pre- and post-surgery. The sexuality part (PIS-Q SF, not shown in a table) did not show any relevant differences pre- and postoperatively

No differences were found in baseline characteristics between the "success" and "failure" patients (Table 5). However, it was found that a BMI of 35 or higher was negatively related to the success rate of the MiniArc (Table 6).

Table 5 Clinical characteristics of failures versus success 1 year after MiniArc (n=57), p<0.05= significant

	Success (dry) (n=25)	Failure (not dry) (n=32)	p value[a]
Age	52.0±12.0 (range, 36–79)	56.0±13.5 (range, 29–80)	0.248
BMI	27.2±4.1 (range, 19.5–33.5)	29.70±7.6 (range, 17.9–50.4)	0.122
Parity	2.0±0.8	2.3±1.0	0.200
None	1 (4%)	1 (3%)	
1–3	23 (92%)	29 (91%)	
>4	1 (4%)	2 (6%)	
Education	3.7±1.7	3.3±1.7	0.309

Values are given as mean ± SD or percentage. Education rated from 1 (primary school) to 7 (university degree). BMI Body mass index in kilograms/square meter [a]Independent-samples *t*-test

Table 6 Sub-categorical success and improvement rates 1-year post-surgery

	Success (dry)				Success (dry)	p value[a]
Complete population	44% (n=57)	vs.	BMI≥35 kg/m^2	(n=7)	0%	0.000[b]
Complete population	44% (n=57)	vs.	Age≥65 years	(n=15)	33%	0.347
Complete population	44% (n=57)	vs.	Parity≥3	(n=14)	40%	0.181
	Improved		**Improved**			**p value[b]**
Complete population	86% (n=57)	vs.	BMI≥35 kg/m^2	(n=7)	57%	0.023[a]
Complete population	86% (n=57)	vs.	Age≥65 years	(n=15)	73%	0.200
Complete population	86% (n=57)	vs.	Parity≥3	(n=14)	86%	0.368

Values are given as percentages. BMI Body mass index, Improved as stated in questionnaire (independent of success). [a]Independent-samples *t*-test, [b]Statistically significant.

Discussion

This prospective single-center study was designed to evaluate the efficacy, safety and impact on quality of life of the MiniArc procedure in women with SUI. Of the 57

evaluated patients, after 1 year, 32 (56%) stated that they were still experiencing SUI, thus indicating failure of the MiniArc. After 1 year, the PGI-I showed an improvement in 68% of the patients (Table 3). Following surgery, an improvement was seen in everyday functioning, as well as a significant drop in incontinence related distress. The DDI part of the questionnaire did not show any significant improvements but was not specifically associated with SUI. For the significant change in the subcategory "genital prolapse" of the UDI, no explanation could be found, but the improvement could be accredited to a decrease of complaints in general. Complications were seen in 6 of 77 patients (8%). The rate of complications and success did not show any significant improvement in time (Table 2). There are certain limitations to this study that need to be addressed.

At present there is an ongoing discussion about the amount of compression with which the mini-slings should be positioned against the urethra. Up to now, no consensus seems to be reached about a standardized method to place these mini-slings as effectively as possible.

Because all the surgeries in this study were performed by one gynecologist (IMC), this could partly explain the lower success rate. However, the gynecologist that performed the surgery is an experienced specialist in MUS surgery, as well as an AMS trained instructor for the placement of the MiniArc. Nevertheless, we recommend this study to be repeated in a multicenter setting using comparative patient groups.

The second limitation is the subjective definition of failure in this study. This subjective measurement, however, does provide information about the experience of the patient over a longer period of time. So, despite the fact that clinical tests after 1 year (Cough Stress Test (CST), pad test, urodynamic investigation) would have guaranteed objectivity, these investigations would merely reflect a measurement at one point in time. We therefore feel that our definition of cure (and failure) is valid to use

Thirdly, it is possible that a misinterpretation of the questions regarding the different types of incontinence could have resulted in inaccurate results. At least part of the patients indicating persistent SUI after 1 year could in fact be experiencing (de novo) urge incontinence. Although we feel that the question in the UDI regarding SUI is clear, clinical tests will be needed to further validate the results and exclude a possible bias.

The major advantage of this study is that multiple questionnaires were used to assess the different improvement or deterioration aspects post-surgery. According to the International Continence Society and the International Consultation on Incontinence, the UDI and the IIQ are recommended as grade A condition specific questionnaires to be used in research (23).

Furthermore the PGI-I and the PIS-Q are recommended by the International Urogynecological Association as validated SUI outcome measures (24). The extensiveness and many different aspects of the questionnaires should make this study valid to offer urologists and gynecologists reliable information.

Due to the fact that prior to the first included patient, our gynecologist had only performed five MiniArc interventions, a learning curve was expected. However, upon analysing the success and failure rates, no improvement in cure and complication rate was found (Table 2). The absence of a learning curve should lead to more reliable and valid results.

For our comparison with other studies, a literature research was conducted in PubMed using the terms "SUI" and "Mini Arc." The found studies for the MiniArc showed success rates ranging from 69% to 91% (11;12;14-17) and are visualized in Table 7. Our 1-year analysis showed different results with a success rate as low as 44%. It is clear that the success rate of our study is exceptionally low, but two other studies (Sottner et al. (17) and Debodinance et al. (12)) also present low rates of success.

Table 7 Other MiniArc studies ranked by number of patients

Study	Number of patients	Success rate (percentage)	Definition of success	Follow-up
Kennelly, MJ, et al. [15]	188	90.6	Negative CST	1 year
Jiménez Calvo J, et al. [14]	135	91.9	Negative CST	495 days (mean)
Pickens RB et al. [18]	120	93.5[a]	Subjective: no leakage	1 year
Hogewoning, CRC, et al.[a]	77	44[a]	Subjective: no leakage	1 year
De Ridder, D, et al. [11]	75	85	Negative CST	1 year
Debodinance, P, et al. [12]	72	69.1	Negative CST	1 year
Moore, RD, et al. [16]	61	91.4	Negative CST	1 year
Sottner, O et al. [17][a]	38	76.7[a]	Subjective: no leakage	19 months

a No objective outcome measures

Variances between subjective and objective outcomes are common in literature, but results are conflicting (25-29). No statement can be made whether subjective success rates deviate from objective ones in either a negative or positive way. Future research should include both objective and subjective measurements that can then be either analysed separately or combined.

Characteristics of the patient population could also partly explain the disappointing success rate. In this study, no restrictions were made based on the severity of SUI and BMI whereas certain other studies leave out patients with a BMI >35 kg/m2. The differences between the "success" and "failure" population are visualized in Table 5 and do not show any significant differences in clinical characteristics.

If the population is further subdivided in specific categories (Table 6), it is shown that a BMI of 35 kg/m^2 or more is an indication for a lower success rate, but higher age (≥65) or a higher number of parities (≥3) is not related to lower rates of success. Improvement

rates in Table 6 also show that a BMI ≥35 kg/m^2 is a significant negative factor in this research population.
The 20 patients (26%) that were lost to follow-up could play a significant part in the accuracy of the evaluation as well, although their characteristics did not show any differences from the participating group.

Conclusion

The 1-year follow-up of the anti-incontinence treatment using the MiniArc single incision sling revealed a high rate of failure (56%), while showing improvement in 68%.

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Results of sling surgery in a non-selected population

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4

Introduction

Urinary incontinence is a condition that affects women worldwide and reduces quality of life (QoL) (1). Stress urinary incontinence (SUI) is the most common type of urinary incontinence and is described as the involuntary loss of urine on effort or exertion, sneezing, or coughing (2). SUI can be treated either conservatively or surgically. The most common conservative treatment options for SUI include lifestyle changes, pelvic muscle exercises (Kegel exercises), physical therapy, biofeedback therapy, or the use of a pessary (3). If conservative treatment fails, the physician and patient can opt for surgical treatment. The European Association of Urology recommends the use of mid-urethral slings (MUSs) as the initial surgical intervention for women with uncomplicated SUI (grade A recommendation) (4). First- and second-generation MUSs, the tension-free vaginal tape (TVT), tension-free vaginal tape-obturator (TVT-O) and trans-obturator tape (TOT), have led to reported cure rates ranging from 84 to 100%, with few complications after a minimum follow-up of 1 year (5-8).

When considering surgery, patients are provided with brochures that usually describe high success rates with few complications on the basis of previous results. Nevertheless, despite vast research on sling surgery over the past decade, studies often lack sufficiently large and representative populations (9-12). Moreover, objective and subjective definitions of cure and improvement often prove variable, and standardized means of evaluation pre- and post-MUS surgery continue to be optional. The aim of the present study was to evaluate MUS surgery in terms of effectiveness and QoL in a non-selected population, and describe the influence of different coexisting medical conditions on the results of surgery.

Materials and methods

A retrospective cohort study was performed at the specialized pelvic floor center of the Albert Schweitzer Medical Center, Dordrecht, the Netherlands. Women who underwent sling surgery as a result of symptoms of urinary incontinence that were predominantly or solely associated with SUI between January 1, 2010, and January 31, 2012, and who had completed a preoperative questionnaire were eligible for inclusion. No restrictions were made regarding age, body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), type of MUS, symptom severity, obstetric or surgical history, or concomitant pelvic organ prolapse (POP). The study protocol was approved by the medical ethics review board of the Albert Schweitzer Hospital, Dordrecht. Participants provided written informed consent.

Before surgery, patients underwent a routine preoperative assessment consisting of a bladder diary, evaluation of urethral mobility and POP, uroflowmetry, a cough stress test, and cystoscopy. As part of the routine preoperative procedure, patients completed a standardized questionnaire. The questionnaire was designed by the Dutch Association for Obstetrics and Gynecology in cooperation with the Dutch Association of Urology to evaluate the impact of urinary incontinence. The questionnaire consisted of an initial QoL scale to evaluate general QoL, the five-dimensional EuroQol instrument (EQ-5D) (13), and a visual analog scale. Subsequent parts evaluated the distress caused by urogenital related symptoms using sections of the Urogenital Distress Inventory (UDI) and the impact of the incontinence on normal daily functioning using the Incontinence Impact Questionnaire (IIQ) (14).

All procedures were performed by one of five experienced pelvic floor surgeons (four gynecologists, one urologist). The slings used were the TVT (Ethicon Gynecare, Cincinnati, OH, USA), TVT-O (Ethicon Gynecare, Cincinnati, OH, USA), TOT (Cousin Inc., Wervicq-Sud,France), and Pelvilace suburethral sling (C. R. Bard Inc., Murray Hill, NJ, USA). The decision regarding which sling to use was made solely on the basis of the physicians' preference and not on patient characteristics. After surgery, a request to use data from the preoperative questionnaire and a postoperative questionnaire were sent to patients by post. The postoperative questionnaires were sent at two points during follow-up (January 2012 and July 2012) to limit differences in time since surgery. In addition to the scales included in the preoperative questionnaire, the postoperative questionnaire included the Patient Global Impression of Improvement (PGI-I) (15). Patients with repeat sling surgery before completion of the postoperative questionnaire or who had died at the time of follow-up were excluded.

For further analysis, the study population was divided into four groups. Patients in group A had no history of either POP or MUS surgery and were solely treated for their SUI; this group was considered to be affected by the fewest confounding variables of the four and was used as the reference group in the later analysis. Patients in group B had a history of POP surgery or vaginal hysterectomy; those in group C had had previous MUS surgery; and those in group D had concomitant POP surgery. Patients could qualify for inclusion in more than one group. The final stage of the analysis evaluated BMI as a possible confounding variable.

Primary outcome measures were the effects of surgery as assessed by the UDI, IIQ, and QoL scales. Patients scoring 0 in the UDI stress symptoms section were considered cured (as recommended by the International Continence Society (16;17)). The subjective improvement or deterioration in symptoms were scored using the PGI-I. If a patient stated her incontinence status as either being "very much improved" or "much improved" after surgery, symptoms were considered improved. The UDI and IIQ were scored using the different subscales as described by van der Vaart et al. (18); outcomes were converted

to a scale from 0–100, with higher values correlating to more severe symptoms. The QoL scale score was converted to a scale from 0–10, with 10 being the highest QoL possible. Statistical analysis was performed using SPSS release 20.0 for Windows (IBM, Armonk, NY, USA). Outcomes were considered significant at the 95% level ($P \leq 0.05$).

Results

Of the 301 women who underwent MUS surgery between January 2010 and January 2012, 255 (84.7%) were included in the present study. Of the 46 patients excluded, 36 had failed to complete the preoperative questionnaire, seven had a second procedure before the postoperative questionnaire was completed, and three were deceased (natural causes). Baseline characteristics are shown in Table 1. No significant differences were found in baseline characteristics between participants and non-participants (data not shown). Among participants, the procedures had been performed under spinal anaesthesia in 109 patients (42.7%) and under general anaesthesia in 146 patients (57.3%).

Table 1 Patient characteristics (N=255)[a]

Age (years)	53.2 ± 12.1 (27.0-85.8)
Body Mass Index[b]	28.3 ± 6.0 (18.9-62.5)
Mixed urine incontinence[c]	204 (79.4)
Concomitant POP surgery (Group D)	98 (38.4)
Vaginal hysterectomy	5 (2.0)
Anterior colporrhaphy	41 (16.1)
Posterior colporrhaphy	62 (24.3)
Sacrospinous fixation	5 (2.0)
Anterior mesh	5 (2.0)
Posterior mesh	7 (2.7)
Manchester fothergill	1 (0.4)
Type of MUS	
TVT	31 (12.2)
TVT-O	55 (21.6)
TOT	158 (62.0)
Pelvilace suburethral sling	11 (4.3)

Abbreviations: POP, pelvic organ prolapse; MUS, midurethral sling; TVT, tension-freevaginal tape; TVT-O, tension-free vaginal tape-obturator; TOT, trans-obturator tape.
a Values are given as mean ± SD (range) or number (percentage).
b Calculated as weight in kilograms divided by the square of height in meters.
c As described in Urogenital Distress Inventory.

Adverse events were seen in 25 (9.8%) of the 255 patients. Six patients needed surgical release of their sling as a result of evident obstructive micturition (four cases), graft erosion (one case), or serious groin pain (one case). Two cases of perioperative bladder-wall perforation and one case of urethral injury were noted. Postoperatively, a para-urethral abscess was found in one patient, and short-term catheterization because of retention or residual volume was necessary in 15 patients. De novo urge urinary incontinence, as assessed by the relevant section in the UDI, was not noted.

The postoperative questionnaire was completed and returned by 228 (89.4%) patients (although three patients did not complete the PGI-I).The mean time since surgery was 14.9 months (range 2–32). UDI, IIQ, and QoL scores all improved significantly after surgery (Table 2). At the time of follow-up, 158 (69.3%) patients were deemed to have been cured according to the UDI. On the PGI-I, 155 (68.9%) of 225 patients reported that their symptoms were very much or much improved, whereas 70 (31.1%) reported only a slight improvement, no difference, or a deterioration (Table 3).

Table 2 Pre- and postoperative scores[a]

	Preoperative N=255	Postoperative N=228	P value[b]
Urogenital symptoms related distress (UDI) total[c]	34.8 ± 16.3	14.9 ± 14.1	<0.001
Discomfort/pain	34.0 ± 28.8	16.2 ± 21.3	<0.001
Urinary incontinence	61.9 ± 24.1	18.6 ± 24.3	<0.001
Overactive bladder	41.5 ± 29.9	21.4 ± 25.6	<0.001
Obstructive micturition	24.1 ± 27.0	17.0 ± 21.9	<0.001
Genital prolapse	12.8 ± 22.5	2.6 ± 8.7	<0.001
Impact on everyday functioning (IIQ) total[c]	30.5 ± 22.0	13.4 ± 17.5	<0.001
Mobility	37.3 ± 27.8	19.7 ± 24.6	<0.001
Emotional	33.5 ± 26.3	15.4 ± 21.6	<0.001
Physical	26.4 ± 28.4	9.8 ± 19.1	<0.001
Social	18.7 ± 22.6	8.7 ± 16.9	<0.001
Embarrassment	38.0 ± 29.8	15.7 ± 23.4	<0.001
QoL scale[d]	4.6 ± 1.1	4.8 ± 1.1	0.014

a: Values are given as mean ± standard deviation. b: Paired-samples *t*-test for continuous data; Pearson X2 test for categorical data. c: Scaled from 1 (no complaints) to 100 (several complaints). d: Scaled from 1 (very bad) to 6 (excellent).

The next phase of the analysis divided the total study population into four groups. Among the 255 patients, 96 (37.6%) were treated for SUI only and did not have a history of either POP or MUS surgery (group A), 81 (31.8%) had a history of POP surgery (group B), 24 (9.4%) had a second MUS (group C), and 98 (38.4%) underwent concomitant POP surgery (group D).

Table 3 Outcomes on the UDI and PGI-I scales

Outcome	No. (%)
UDI (n = 228)	
Cure	158 (69.3)
Failure	70 (30.7)
PGI-I (n = 225)[a]	72 (32.0)
Very much improved	83 (36.9)
Much improved	37 (16.4)
A little improved	12 (5.3)
No difference	13 (5.8)
A little worse	4 (1.8)
Much worse	4 (1.8)
Very much worse	4 (1.8)

Abbreviations: UDI, Urogenital Distress Inventory; PGI-I, Patient Global Impression of Improvement.
a: Three patients failed to complete the PGI-I postoperatively.

The first sub-analysis compared the group of patients with a history of either POP surgery or hysterectomy (group B) and group A, and showed significantly worse scores regarding both improvement and the UDI score, although cure rates did not differ (Table 4). Compared to patients in group A, those in group B had a higher mean age (59.4 vs 50.5 years; P ≥0.05) and a higher prevalence of pre-existent mixed urinary incontinence (70 [86.4%] of 81 vs 71 [74.0%] of 96; P ≥0.05).

Table 4 Postoperative outcomes in the four subgroups[a,b]

Outcome	Group A	Group B	Group C	Group D
	(n = 79)	(n = 78)	(n = 22)	(n = 90)
UDI total[c]	11.3 ± 11.1	19.3 ± 15.7[d,e]	23.5 ± 14.7[d,e]	14.7 ± 13.3
IIQ total[c]	12.3 ± 17.7	17.8 ± 19.5	26.9 ± 22.8[d,e]	13.1 ± 17.0
QoL scale[f]	4.8 ± 1.1	4.6 ± 1.1	4.3 ± 1.3	4.9 ± 1.0
EQ-5D[g]	88.0 ± 16.4	85.6 ± 18.6	82.3 ± 17.5	87.7 ± 14.4
VAS[h]	77.8 ± 16.0	75.3 ± 17.3	70.5 ± 16.7	76.7 ± 14.8
Cure[i]	56 (70.9)	49 (62.8)	8 (36.4)[d,j]	68 (75.6)
Improvement[k]	57 (74.0)	44 (57.1)[d,j]	6 (28.6)[d,j]	65 (72.2)

Abbreviations: UDI, Urogenital Distress Inventory; IIQ, Incontinence Impact Question- naire; QoL, Quality of life; EQ-5D, EuroQol-5 Dimensions; VAS, Visual Analog Scale.
a: Values are given as mean ± standard deviation or number (percentage). b: Group A, reference group; group B, patients with a history of prolapse surgery or hysterectomy; group C, patients with previous midurethral sling surgery; group D, patients undergoing concomitant pelvic organ prolapse surgery. c: Scaled from 1 (no complaints) to 100 (a lot of complaints). d: Comparison with group A: P <0.05. e: Independent-samples *t*-test. f: Scaled from 1 (very bad) to 6 (excellent). g: Based on Dutch values: utility score from 1 (very bad) to 100 (excellent). h: Scaled from 1 (very bad) to 100 (excellent). i: Score of 0 on UDI. j: $\chi 2$ test. k: Incontinence status "very much improved" or "much improved" according to the PGI-I.

Comparison between groups C (repeat sling surgery) and A showed significantly lower cure and improvement rates in group C (P < 0.001) as well as higher scores on both the UDI (P = 0.018) and IIQ (P = 0.017) (Table 4). Patients in group C were also older (56.1 vs 50.5 years; P = 0.048) and had a higher BMI (30.0 vs 27.6), although the difference was not significant.

The postoperative scores of group D (patients with concomitant POP surgery) showed no significant differences in patient-reported cure and improvement rates when compared with group A (Table 4). Postoperative UDI, IIQ, and QoL scores of Group D did not differ significantly from those of group A (Table 4). No differences in demographics were seen between groups A and D (data not shown).

The final analysis compared patients with regard to BMI, showing that women with a BMI of at least 35 scored significantly worse in several sections of the questionnaire, although the cure rate did not differ significantly (Table 5).

Table 5 Postoperative outcomes of patients according to BMI[a,b]

Outcome	BMI <35	BMI ≥35	P value[c]
	(n = 189)	(n = 17)	
UDI[d]	12.9 ± 13.1	24.0 ± 12.1	0.005
IIQ[d]	12.1 ± 15.6	16.7 ± 24.4	0.448
QoL scale[e]	4.8 ± 1.0	4.3 ± 1.2	0.076
EQ-5D[f]	89.1 ± 14.1	69.7 ± 29.1	0.015
VAS[g]	78.1 ± 15.4	66.5 ± 14.8	0.008
Cure[h]	139 (73.5)	11 (64.7)	0.409
Improvement[i]	141 (74.6)	8 (47.0)	0.041

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); UDI, Urogenital Distress Inventory; IIQ, Incontinence Impact Questionnaire; QoL, Quality of life; EQ-5D, EuroQol-5 Dimensions; VAS, Visual Analog Scale.

a: Values are given as mean ± SD or number (percentage), unless indicated otherwise. b: Patients who underwent secondary midurethral sling surgery were excluded. c: Paired-samples *t*-test for continuous data; Pearson $\chi 2$ test for categorical data. d: Scaled from 1 (no complaints) to 100 (a lot of complaints). e:Scaled from 1 (very bad) to 6 (excellent). f: Based on Dutch values: utility score from 1 (very bad) to 100 (excellent). g: Scaled from 1 (very bad) to 100 (excellent). h: Score of 0 on UDI. i: Incontinence status "very much improved" or "much improved" according to the Patient Global Impression of Improvement.

Discussion

The present study has evaluated MUS surgery in a non-selected population using a combination of standardized, validated questionnaires both before and after surgery.

Overall, approximately 70% of the study population reported positive effects of the intervention (either cure or improvement). Moreover, nearly all incontinence-related symptoms improved after surgery. Subgroup analysis showed multiple differences between the patient groups with and without confounding variables. It was observed that patients with prior sling surgery benefited significantly less from an intervention than did those in the reference group. Moreover, patients with a history of POP surgery showed significantly less improvement postoperatively, although cure rates did not differ. The analysis of patients with concomitant POP surgery showed comparable scores in all outcome parameters postoperatively. Further analysis showed that, although a higher BMI influences improvement rates and several other aspects of SUI postoperatively, it does not have a negative effect on the success of surgery.

The present study found slightly lower cure rates than those described in a meta-analysis by Schimpf et al. (8), which presented subjective cure rates ranging from 43 to 100%. One explanation for the lower cure rates observed is the fact that no restrictions were made regarding age, BMI, type of MUS, symptom severity, obstetric or surgical history, or concomitant POP. Lower cure rates have also been observed in other studies using similar inclusion criteria (10;19). Moreover, cure rates defined by validated subjective measures tend to be lower than those defined by objective measures (20).

In recent years, there has been ongoing discussion regarding whether to combine MUS and POP surgery (21). The present study suggests that simultaneously performing POP and MUS surgery has no negative effect on the outcome in terms of SUI-related symptoms. Several previous studies have described simultaneous POP surgery and MUS placement (21-23). All authors supported the combined procedures, as they provided significant improvements in both urinary symptoms and QoL. In the review by van der Ploeg et al. (21), the authors conclude that combined surgery (POP and MUS) is beneficial and should be considered in women with both POP and SUI, although the number of adverse events could be higher.

The analysis of patients with repeat sling surgery showed that this group performed significantly less than women receiving a primary MUS. Other studies have also observed low success rates after repeat sling surgery (24;25); however, the success rates found in the present investigation are the lowest. This discrepancy could be due to the fact that in the present study women had a higher BMI and age or had genuine urethral sphincter deficiency instead, although this was not specifically analysed.

The European Association of Urology guidelines on the surgical treatment of urinary incontinence (4) indicate that both age and BMI are possible confounding variables determining the success of a surgical intervention. Studies on MUS surgery frequently exclude patients with a BMI of more than 35 because an intervention is expected to be less effective in this group (26;27). This expectation is supported by several parts of the

present analysis, although not with regard to the success rate; however, because only 17 patients had a BMI of over 35, no conclusions can be drawn.

The main strength of the present study is the use of multiple questionnaires, with a response rate of 89.4% at the time of follow-up. This contributed to an extensive results section in which multiple confounding variables could be analysed separately. The major limitation of the present study was the fact that no objective methods were used to determine the effects of surgery and, although a cough stress test or pad test merely represent a measurement at one point in time, these would have objectified the findings. Future research should therefore include both objective and subjective measurements that should then be analysed separately and in combination. The second limitation is the fact that several types of MUS (TVT, TVT-O, and TOT) and techniques (retropubic and trans-obturator) were used but were not analysed separately. Although this limitation could possibly bias the results, the meta-analysis conducted by Schimpf et al. (8) does recommend either retropubic or obturator slings for cure outcomes. Finally, because the postoperative questionnaires were sent at only two points, the range of time since surgery is large. Although this large range makes results more difficult to interpret, the overall mean follow-up period of 14.9 months should ensure reliable information.

In conclusion, MUS surgery is both efficient and effective in curing SUI. However, the present study shows that patient characteristics and confounding variables can greatly influence the outcome of surgery. The use of multiple validated questionnaires results in a multifaceted database that can then be used by physicians to provide optimal informed consent before MUS surgery.

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Results of collagen sling placement following the partial removal of a synthetic mid-urethral sling

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Introduction

Urinary incontinence among women is a common problem that places a large demand on healthcare resources in high-income countries (1;2). Stress urinary incontinence (SUI) is described as the involuntary leakage of urine on a rise in abdominal pressure and is associated with a negative impact on sexual, psychological, and social functioning (3;4). In 1995, the tension-free vaginal tape (TVT), a polypropylene sling used through a minimally invasive technique to cure SUI, was introduced by Ulmsten and Petros (5). Because of its high success rates and few complications, the TVT soon became the leading surgical treatment for SUI. Following the successful application of the TVT, the trans-obturator tape was introduced in 2001, followed by the TVT Obturator in 2004 and mini-slings in 2006 (6;7). In the past decade, a vast number of mid-urethral slings (MUS) have been developed, with millions of (mostly successful) interventions having been performed worldwide (8:9).

Although most vaginal slings boast low complication rates, serious complications have nevertheless been associated with their use; such complications should always be taken into consideration by both physicians and patients (8). According to the 4th International Consultation on Incontinence (10), vaginal sling complications can occur during surgery (mostly hemorrhage and injury to the lower urinary tract) or after the procedure (much more diverse in nature).

Available data on the rate of (late) postoperative complications following MUS surgery indicates that the frequency of these complications is generally low (8). The most commonly occurring postoperative complications are erosion of the mesh material, displacement of the tape, infection, and pain. Although local treatment of these complications is possible in some patients, in others, eventual complete or partial removal of the mesh is unavoidable. Since the introduction of MUS in the treatment of SUI, multiple reports have described the results and complications, but only a limited number have concerned the treatment of (late) postoperative complications. More importantly, in the current literature, no consensus has yet been reached on the proper treatment of these complications.

The Pelvilace collagen sling is a porcine xenograft acellular matrix bio-implant that can be chosen as a secondary sling to minimize the risk of rejection and to fill in the anatomical defect caused by removal of the primary sling (11). The present study evaluates the results of Pelvilace collagen sling placement directly following partial removal of a primary sling because of late complications.

Materials and methods

A retrospective study was undertaken of patients experiencing late complications following MUS surgery who underwent placement of a Pelvilace collagen sling (C.R. Bard Inc., Murray Hill, NJ, USA) after partial removal of a primary sling at the Albert Schweitzer Medical Center Dordrecht, the Netherlands, between January 1, 2006, and January 31, 2011. The study center is a tertiary referral center treating MUS complications from all around the Netherlands. Exclusion criteria were the placement of the Pelvilace collagen sling as primary treatment or receiving a third suburethral sling within the follow-up period. The study protocol was approved in March 2012 by the medical ethics review board of the Albert Schweitzer Hospital. Participants provided written informed consent.

All surgery had been performed by the same urogynecologist (C.J.A.H.) in the specialized pelvic floor center of the Albert Schweitzer Medical Center. The primary tapes involved were the Intra-Vaginal Sling (Tyco Healthcare, Dublin, Ireland [Covidien from 2007]), TOT Intramesh Softlift (Cousin Biotech, Wervicq-Sud, France), Uretex-TO (C.R. Bard Inc, Murray Hill, NJ, USA), and the TVT and TVT Obturator (Ethicon Women's Health and Urology, Johnson and Johnson, New Brunswick, NJ, USA).

All patients received spinal anesthesia and were placed in the lithotomy position. The first step consisted of the dissection of the anterior vaginal wall, after which the sling was bilaterally removed as far as the internal obturator muscle for trans-obturator slings and the pubic bone for retropubic slings. Following partial removal, the remaining mesh and adjacent tissue were examined for signs of infection or erosion and a routine cystoscopy was performed. Next, the Pelvilace collagen sling was placed in the defect left by the removed tape in the case of erosion or in the correct suburethral position in the case of displacement, followed by a cough stress test to tune the tension of the tape. The tape was placed outside-in through the obturator foramen using a similar technique as described by Delorme et al. (7). The sling was superficially fixated on the suburethral tissue using a slow resorbable stitch (PDS 3-0) and the anterior vaginal wall was closed. Patients were given a transurethral catheter for at least 1 day and prophylactic antibiotics were administered during the first postoperative week.

Between April 2012 and October 2014, identified patients were sent questionnaires that had been designed specifically for the present study. Questionnaires were sent at different times to minimize variation in the length of time since surgery. Patients who had not responded to the previous request were re-contacted the next time questionnaires were sent.

Urodynamics were conducted when urethral instability was suspected before the secondary surgery, including a measurement of the maximum urethral closure pressure (MUCP), before and at least 6 months after repair, as well as an evaluative cystoscopy.

The questionnaire was assembled using a combination of various validated and non-validated questionnaires. It consisted of 44 questions divided into 6 sections evaluating improvement/deterioration, physical condition (health status), micturition, coping behavior (emotional status), and sexual functioning. The Patient Global Impression of Improvement (PGI-I) represented the first part of the questionnaire and assessed the subjective improvement/deterioration after surgery; patients stating their incontinence status as either being "very much better" or "much better" were considered improved. The second part included a visual analogue scale (VAS) and QoL scale to evaluate overall health status. Micturition status and pelvic floor dysfunction were assessed in the third part of the questionnaire using sections of the Urinary Distress Inventory (UDI) and Pelvic Floor Distress Inventory (12-14). Patients scoring 0 in the UDI stress symptoms section were considered cured (as recommended by the International Continence Society). The fourth part scored the coping behavior using the Incontinence Impact Questionnaire (IIQ) (12;13). Both the IIQ and UDI were scored using the different domains as described by van der Vaart et al. (15). Sexual functioning was assessed using 14 non-validated questions designed by the Pelvic Floor and Sexuality Research Group in Leiden. The last question asked the patient whether she would recommend this intervention to patients experiencing similar problems.

The results were statistically evaluated using paired and independent samples *t*-tests in SPSS release 21 (IBM, Armonk, NY, USA). P ≥0.05 was considered statistically significant.

Results

Between January 2006 and January 2011, 38 patients received the Pelvilace collagen sling after partial sling removal and were included in the study (Figure 1). The patients' baseline characteristics are shown in Table 1. The primary sling types and the complications leading to the placement of Pelvilace are described in Table 2. No adverse events were observed during or directly following the placement of the Pelvilace collagen sling.

Table 1 Baseline characteristics (N=38)

Age (years)	54.7 ± 10.5 (27-81)
BMI (kg/m^2)[a]	27.6 ± 4.4 (18.2-37.4)
Mean follow-up[b]	54.3 ± 17.1 (17-89)

a: Derived from questionnaire, n=32 and calculated as weight in kilograms divided by the square of height in meters. b: Period between surgery and questionnaire, n=29,

The questionnaire was completed and returned by 32 (84%) patients. No significant differences were observed in baseline characteristics between responders and non-responders (data not shown). Three patients were excluded from further analysis following the placement of a third sling during the follow-up period because of persistent SUI (Figure 1). These patients were included in the success/failure rates as failures to avoid bias.

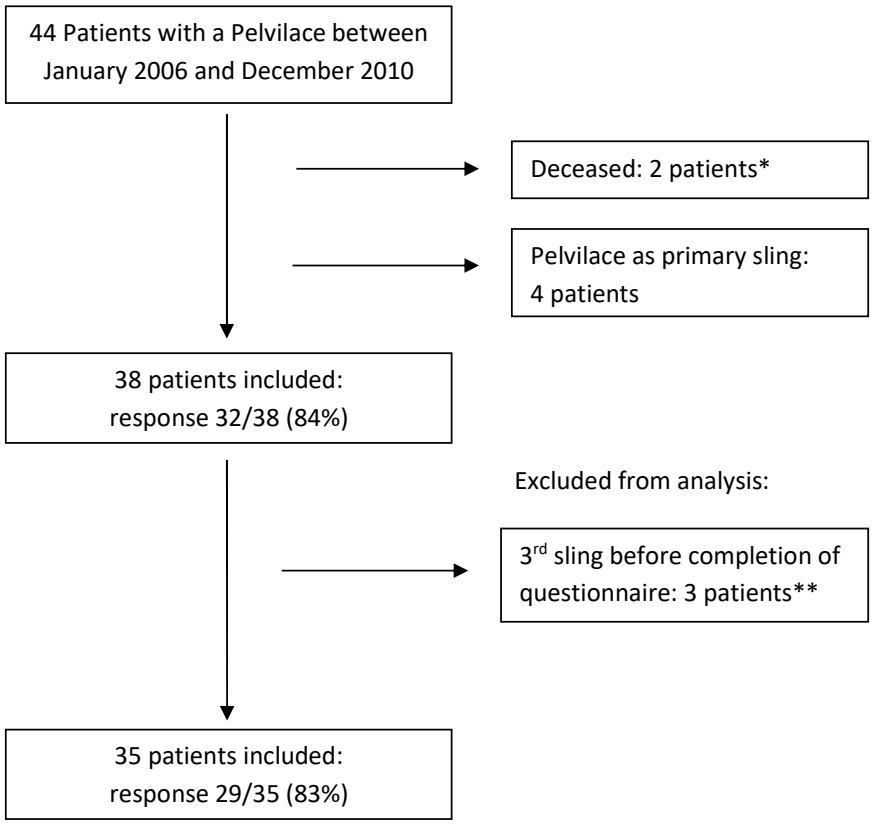

Figure 1 Flow of patients through the study
*Death not due to Pelvilace placement
**These patients were included in the failure/success analysis as failures

Table 2 Types of primary slings and complications[a]

Type of primary sling	All patients	Complications after primary sling placement		
		Erosion (n=15	Displacement (n=13)	Both (n=10)
Tension-free Vaginal Tape	12/38 (32)	8/12 (67)	2/12 (17)	2/12 (17)
Uretex-TO	9/38 (24)	1/9 (11)	5/9 (56)	3/9 (33)
TOT Intramesh Softlift	7 (18)	1/7 (14)	3/7 (43)	3/7 (43)
Intravaginal Sling	4 (11)	2/4 (50)	1/4 (25)	1/4 (25)
TVT-Secur	4 (11)	3/4 (75)	0/4	1/4 (25)
Tension-free Vaginal Tape-Obturator	2 (5)	0/2	2/2 (100)	0/2

Values are given as number (percentage)

More than one-quarter of the 32 women included in analysis of success and failure reported being cured on the UDI (Table 3). Among the 29 women eligible for further analysis, the PGI-I showed a postoperative improvement in approximately half (Table 3). The remaining 15 (52%) patients rated their postoperative status as little improved, unchanged, or deteriorated.

Table 3 Cure/failure according to the UDI and improvement acoording to the PGI-I., by complications after primary sling placement[a]

	All women	Erosion (12)	Displacement (9)	Both (11)
UDI[b]				
Cure	9 (28)	4 (33)	0	5 (45)
Failure	23 (72)[a]	8 (67)	9 (100)	6 (55))
PGI-I[c]				
Very much better	8 (28)	4 (33)	1 (13)	3 (33)
Much better	6 (21)	4 (33)	1 (13)	1 (11)
A little better	4 (14)	2 (17)	2 (25)	0
No difference	6 (21)	2 (17)	3 (38)	1 (11)
A little worse	2 (7)	0	1 (13)	1 (11)
Much worse	0	0	0	0
Very much worse	3 (10)	0	0	3 (33)
Improvement [d]	14 (48)	8 (67)	2 (25)	4 (44)
No improvement[e]	15 (52)	4 (33)	6 (75)	5 (56)

Abbreviations: UDI, Urinary Distress Inventory; PGI-I, Patient Global Impression of Improvement.
a Values are given as number (percentage).
b n=32 (12 with erosion, 9 with displacement, 11 with both). Includes the 3 patients who had a third sling placed before the time of the postoperative questionnaire as failures.
c n=29 (12 with erosion, 8 with displacement, 9 with both),
d Very much better or much better.
e A little better, no difference, a little worse, much worse, or very much worse.

Postoperative improvement according to the PGI-I was most often observed among the 12 women who underwent Pelvilace placement as a result of erosion (Table 3). Scores on the UDI, IIQ, QoL scale, and VAS are shown in Table 4. In terms of postoperative sexual functioning, 16 (55%) of the 29 patients stated being completely sexually inactive at the time of follow-up. One of these patients (6%) blamed urinary incontinence during intercourse as the direct cause of her sexual inactivity, whereas 3 (19%) indicated pain as the main reason.

Table 4 Postoperative scores for the UDI, IIQ, quality of life scale and visual analogue scale (n=29)

Questionnaire	Postoperative scores
UDI	
Total	25.2 ± 20.2
Discomfort/pain	21.4 ± 30.4
Urinary incontinence	38.5 ± 30.9
Overactive bladder	32.8 ± 32.3
Obstructive micturition	29.2 ± 31.6
Genital prolapse	3.6 ± 9.5
IIQ	
Total	20.5 ± 23.2
Mobility	32.2 ± 29.0
Emotional	23.4 ± 30.5
Physical	19.05 ± 24.3
Social	13.9 ± 26.1
Embarrassment	20.7 ± 32.6
Quality of life scale	4.4 ± 1.2
Visual analogue scale	6.8 ± 1.9

Abbreviations: UDI,Urinary Distress Inventory; IIQ, Incontinence Impact Questionnaire.
a Values are given as mean ±SD.
b Scaled from 1 (no complaints) to 100 (severe complaints).
c Scaled from 1 (very bad) to 6 (excellent).
d Scaled from 1 (very bad) to 10 (excellent).

When asked whether they would recommend this intervention to other patients under similar circumstances, 19 (66%) of 29 patients answered "yes". The 10 (34%) patients advising against the treatment indicated persistent urinary incontinence as their main reason for doing so.

Table 5 Urodynamics [a]

	Preoperative	Postoperative [b]	P-value [c]
Maximal urethral closing pressure (cmH2O)	42.1 ± 13.4	55.2 ± 17.9	0.001
Maximum flow (ml/s)	25.4 ± 10.8	18.2 ± 8.4	<0.001
Bladder capacity (ml)	411 ± 129	318 ± 72	0.001

a Values are given as mean ± SD unless indicated otherwise
b Conducted at a minimum of 6 months post-surgery
c Paired samples *t*-test.

In 19 (66%) of the 29 patients, a presurgical urodynamic analysis was conducted when urethral instability was suspected and repeated at least 6 months after the placement of the Pelvilace sling. Analysis showed that the MUCP increased significantly after surgery (P=0.001) (Table 5). The maximum flow showed a significant decrease (P <0.001) (Table 5). The postoperative bladder capacity also showed a significant decrease (P=0.001) (Table 5). No significant differences were found in MUCP, maximum flow, and bladder capacity between the patients with success and failure, or with and without improvement (data not shown).

Discussion

The present study showed that 28% of women who underwent placement of a Pelvilace after partial removal of a primary sling reported postoperative success after a mean follow-up of 54.3 months. Almost half of the questionnaire respondents reported improvement. Success and improvement showed no significant differences between women who experienced erosion, displacement, or both after primary sling placement. However, significant differences were observed in urodynamic analysis (maximum flow, MUCP, bladder capacity) before and at least 6 months after surgery. Overall, two-thirds of respondents would recommend this intervention to other patients under similar circumstances. The patients who would not recommend surgery indicated persistent urinary incontinence as their main reason to advise against the treatment.

To correlate the present results with those found in previous studies, a literature search was performed using the MeSH terms "urinary incontinence," "suburethral sling," and "complications". This search produced 939 results, of which none had a design similar to that of the present study. Several studies did discuss partial or complete sling removal, but did not include the subsequent placement of a second tape of porcine dermis (16-18). One paper did approach the present study design by describing 21 patients in whom a primary synthetic sling was removed and replaced by a concomitant sling of

autologous rectus fascia (19); the study achieved continence in 71.5% of the patients with urethral perforation and in 100% of patients with a bladder perforation.
The main outcome variable in the present study was the subjective cure of urinary incontinence after surgery. The results showed an overall postoperative continence rate of 28%, with a maximum cure rate of 45% in the group with both erosion and displacement of the primary sling. A review of the current literature on the management of mesh complications after SUI and pelvic organ prolapse surgery describes a 20% recurrence of SUI after transvaginal MUS excision (20). Although the concomitant placement of a second sling should theoretically enhance continence after primary sling removal, this was not observed in the present study. One explanation for these disappointing results could be the fact that the collagen sling used seems to be less effective in curing SUI in the long term by comparison with conventional polypropylene tapes (21). However, when considering that the present study population involved patients who experienced postoperative complications, the results should not be compared with those of studies in which the Pelvilace collagen sling was used as a primary sling. The second explanation could be the strict definition of success/failure measured solely by the UDI stress symptoms section and the lack of objective measurements. Nevertheless, the UDI represents a patient's experience over an extended period of time and should therefore be relied upon to produce trustworthy information. Moreover, because no comparable studies are currently available, no viable statements can and should be made on whether the success rates found are actually lower than expected.
The most important limitation of the present study is the fact that the patient group was not homogenous. In a tertiary referral center, all complications following MUS surgery are treated, including erosion and displacement. Further, the concomitant placement of the same collagen sling in all patients and their evaluation through the use of the same questionnaire makes it difficult to interpret the results. In an attempt to further clarify the results, the study population was divided into separate groups; nevertheless, the numbers needed to draw viable conclusions are lacking. Finally, the study included 6 different types of primary slings, with small patient numbers for each type. Although a lack of sufficient patient numbers is a common problem when describing rare complications, it does inevitably lead to difficulties in the processing of results.
In conclusion, despite nearly half of patients experiencing an improvement after surgery, only 28% of patients were cured of their SUI after partial sling removal with concomitant placement of a Pelvilace collagen sling. The divergence in the failure rates between different types of complications (erosion and displacement) shows that there is no general approach in the treatment of these complications. Further, as evidenced by an evaluation of the current literature, no consensus has yet been reached on the proper treatment of late postoperative complications following MUS surgery. Although the current study presents reasonable results for specific complications, the solution to

this ever-growing problem remains to be elucidated. More research on the individual approach of specific complications will be needed in the future to provide optimal patient care.

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Sling surgery for the treatment of urinary incontinence after transurethral resection of the prostate: evaluation of literature and new data on the Virtue® male sling

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6

Introduction

One of the most frequently performed surgical procedures for the treatment of obstructive symptoms following benign prostate enlargement is the transurethral resection of the prostate (TURP). Complication rates following a TURP are generally low but are frequently encountered due to large numbers of surgery being performed. Stress urinary incontinence (SUI) is a common complication following a TURP, occurring in 1.8% to 5.0% of the patients (1-4). SUI in these cases is usually caused by damage to the proximal part of the (rhabdo) sphincter distal to the seminal colliculus (or verumontanum) (5).
It is known that SUI has a significant impact on the quality of life (QoL) and when conservative treatment (e.g. pelvic floor physiotherapy) fails, surgical procedures can be considered. The two most common surgical options are the implantation of an artificial urinary sphincter (AUS) or the use of a male sling (6).
Throughout history, multiple surgical techniques have been developed for the treatment of male urinary incontinence. In 1947, Foley introduced an externally worn urethral cuff and subsequent modifications by Kaufman in 1973 led to the first fully internal AUS. Since, the AUS is considered to be the gold standard in the surgical management of urinary incontinence following prostate surgery (7;8). Documented AUS success rates are generally high and vary between 59% and 91.4% (9;10). When complications occur however, surgical revision is often required and AUS explantation rates due to mechanical failure, infection or erosion can be as high as 36% (11;12).
In the search for a less invasive procedure, synthetic male slings have gained popularity in the treatment of mild to moderate SUI. The concept of the male sling for the treatment of SUI is based on a combination of less invasiveness, fewer postoperative complications and a significant cost reduction. Present studies on the efficacy and complication rates of different types of male slings show success rates varying from 40% to 91%, with generally lower complication rates when compared to AUS surgery (13;14). Nevertheless, the majority of these studies only describe male slings after a radical prostatectomy (RP) and little is known on the efficacy of male slings in post-TURP patients specifically.
The Virtue® is a relatively new sling, introduced in 2012 by Coloplast (Humlebaek, Denmark) for the treatment of male SUI. This quadratic male sling combines perineal urethral compression with proximal urethral relocation, making it a hybrid sling. The monofilament polypropylene mesh contains two inferior (trans-obturator) extensions and two superior (prepubic) extensions (15;16).
The first part of this study provides an overview of the available literature regarding male slings in post-TURP patients. Secondly, a prospective study was conducted in a cohort of 8 patients at the department of Urology at the Leiden University Medical Center to assess the effects of the Virtue® sling on patients suffering from post-TURP SUI.

Material and methods

The first part of this paper consists of a review of literature regarding the efficacy of synthetic male slings in patients suffering from post-TURP SUI. The review started with an electronic database search of PubMed, Embase, Web of Science, Cochrane and Cinahl using the search strategy shown in figure 1. One author screened the articles by title, abstract or by full article, when necessary, to select studies that met the predefined selection criteria. Selection criteria were defined as: language (English, German, French or Spanish), mean topic (male sling for urinary incontinence following prostate surgery, including TURP), type (case study, cohort study or randomized controlled trial) and availability of the results (published in peer reviewed journal).

(((("male sling"[tw] OR "male slings"[tw]) AND ("Urination Disorders"[Mesh] OR "Anuria"[tw] OR "Enuresis"[tw] OR "Hematuria"[tw] OR "Haematuria"[tw] OR "Oliguria"[tw] OR "Polyuria"[tw] OR "Urinary Incontinence"[tw] OR "Urinary Retention"[tw] OR "Prostatectomy"[Mesh] OR Prostatectom*[tw] OR ("transurethral"[tw] AND "resection"[tw] AND prostat*[tw]) OR "turp"[tw] OR "Transurethral Resection of Prostate"[Mesh] OR "micturition"[tw] OR "urination"[tw] OR "Urination"[mesh])) OR (("urinary slings"[tw] OR "urinary sling"[tw] OR "urethral sling"[tw] OR "urethral slings"[tw] OR "midurethral sling"[tw] OR "midurethral slings"[tw] OR "periurethral sling"[tw] OR "periurethral slings"[tw] OR "suburethral sling"[tw] OR "suburethral slings"[tw] OR "bulbourethral sling"[tw] OR "bulbourethral slings"[tw] OR "transobturator sling"[tw] OR "transobturator slings"[tw] OR "pubourethral sling"[tw] OR "pubourethral slings"[tw] OR (("sling"[tw] OR "slings"[tw]) AND ("urinary"[tw] OR "urethral"[tw] OR "urogenital"[tw] OR "midurethral"[tw] OR "periurethral"[tw] OR "suburethral"[tw] OR "bulbourethral"[tw] OR "subpubic"[tw] OR "anteropubic"[tw] OR "transobturator"[tw] OR "pubourethral"[tw]))) AND ((("Urination Disorders"[Mesh] OR "Anuria"[tw] OR "Enuresis"[tw] OR "Hematuria"[tw] OR "Haematuria"[tw] OR "Oliguria"[tw] OR "Polyuria"[tw] OR "Urinary Incontinence"[tw] OR "Urinary Retention"[tw] OR "micturition"[tw] OR "urination"[tw] OR "Urination"[mesh]) AND ("Male"[mesh] OR "male"[tw] OR "Men"[mesh] OR "man"[tw] OR "men"[tw] OR "boy"[tw] OR "boys"[tw])) OR "Prostatectomy"[Mesh] OR Prostatectom*[tw] OR ("transurethral"[tw] AND "resection"[tw] AND prostat*[tw]) OR prostat*[tw] OR "Prostate"[Mesh]))))

Figure 1 Search Strategy

The second part of the paper is a prospective clinical trial performed at the Department of Urology of the Leiden University Medical Center as part of a European study on the Virtue® male sling. All patients that underwent surgery using the Virtue® male sling as surgical treatment for post-TURP SUI between January 2012 and November 2013 were included after written informed consent was obtained (n = 8). Exclusion criteria were previous anti-incontinence surgery or prostate cancer. All 8 patients underwent a cystoscopy and urodynamic investigation at baseline to evaluate sphincter function and to rule out detrusor instability and bladder neck strictures. All procedures were performed by a single surgeon using the surgical technique described by Rhee (17).

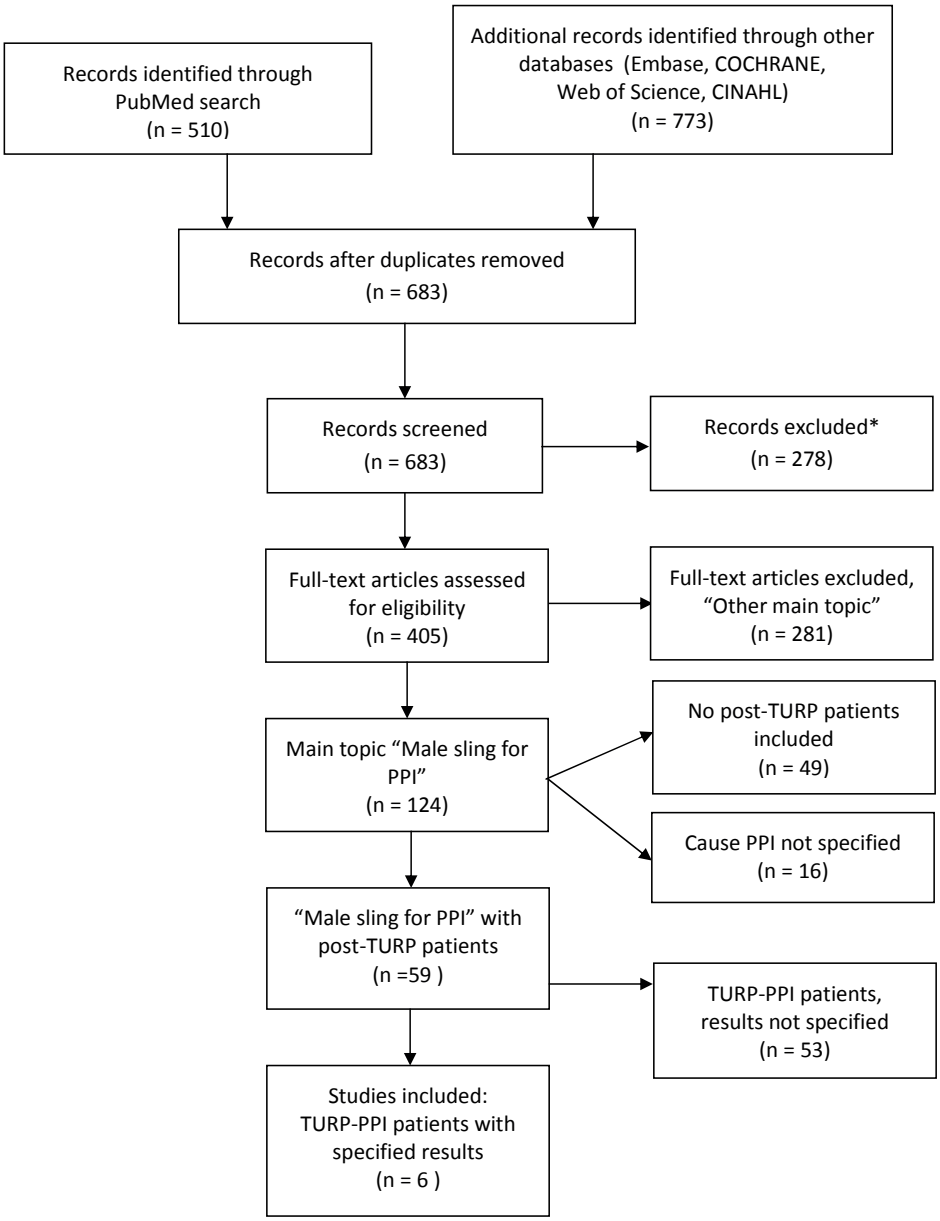

Figure 2 PRISMA flow chart

*Exclusion criteria: animal study, female study, pediatric study, editorial comment, author replies, conference abstract, not "peer-reviewed journal," other language (not English, French, German, Spanish). PPI, postprostatectomy incontinence; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (www.prisma-statement.org).

A pre- and postoperative pad test was used to evaluate continence after surgery. Success was defined as no pad use (0 pads per day; PPD) or the use of one dry "safety pad" only. Improvement was defined as a pad reduction of 50% or more compared to the preoperative situation. In addition, a questionnaire consisting of 40 multiple-choice questions was used for evaluation. The first part included a visual analogue scale (VAS) and specific questions assessing patients' satisfaction regarding the surgery, as well as the usage of pads. The second part consisted of the Dutch translation of the King's Health Questionnaire (KHQ). The KHQ is a validated, condition-specific (urinary incontinence) quality of life questionnaire and is recommended by the European Association of Urology (EAU) as a specific tool for the evaluation of incontinence (18-20). The preoperative questionnaire was identical to the postoperative questionnaire, except for the questions concerning the sling surgery itself. Patients were asked to complete questionnaires preoperatively and 1, 3, 6 months and 1 year postoperatively. The secondary outcomes of our study were QoL, pain and surgery satisfaction measured using the KHQ and VAS questionnaires.

Statistical analysis was performed using SPSS Statistics (Version 20, IBM Corporation, Armonk, NY). The results of the systematic review on slings following a TURP and other prostate related surgery were processed in crosstabs and compared using Fisher exact tests. The pre- and postoperative comparison of the KHQ, VAS, and pad usage was performed with paired two-tailed *t*-tests. $P<0.05$ indicated statistical significance.

The questionnaire used is part of the standard follow-up program for incontinence patients in this center and hence did not require approval by the medical ethics comity.

Results

The first part of this study consisted of a systematic literature search regarding male slings in patients post-TURP. The search strategy retrieved 1283 records of which 59 included patients with post-TURP SUI. Combined, the 59 studies included 2736 patients of which 230 had post-TURP SUI (8,4% of all patients). Six of the 59 studies differentiated between post-RP and post-TURP patients and were eligible for inclusion (see PRISMA flow-chart in figure 2) (21-25). The 6 included studies reported on a combined total of 23 patients. Postoperative success was defined as total continence, a pad reduction of 50% or more, daily loss of urine <2grams, or a subjective improvement in continence stated in an interview. In these 6 studies, post-TURP sling success rates ranged from 0-100% and were significantly lower compared to success rates in patients who did not undergo a TURP (mean 78.3% vs. 95.0%; $p=0.009$, $p<0.05$).

Table 1 Pads per Day

Patients	Preoperative Pads/Day	Postoperative Pads/Day			
Age		1 month	3 months	6 months	12 months
68	>6	0	0	0	0
58	5-6	0	1-2	1-2	1-2
74	5-6	1-2	1-2	1-2	1 sp
74	5-6	1-2	1-2	1-2	1-2
73	1-2	1 sp	1-2	1 sp	1 sp
61	1-2	1-2	1-2	1-2	1-2a
60	1-2	3-4	1-2	1-2	b
75	1-2	0	0	0	0

sp = dry security pad, a: type pad preop "large", 12mo "regular", b: patient had received AUS

The second part of this paper described 8 patients who received the Virtue® sling as surgical treatment for post-TURP SUI between January 2012 and November 2013. No adverse events were observed during or in the 12 months following surgery. The response rate was 100%, but 1 patient was excluded from further analysis after 9 months when he received an AUS because of persistent incontinence. At 12 months postsurgery 4 patients were considered cured, meaning no pad usage or use of 1 dry security pad only. Another 2 patients were considered improved, whereas the 1 remaining patient had no change in PPD, even though pad size was reduced from large to regular. All patients (n=4) who had severe SUI (>5 PPD), experienced a postoperative improvement. Two of these patients had more than 50% pad reduction and the other 2 stated to be completely dry (Table 1).

The pre- and postoperative VAS scores evaluating the influence of SUI on daily life (scored from 0 "not at all", to 10 "very much") were compared using a paired-samples *t*-test. The results showed a significant decrease in the impact of SUI at all intervals in comparison to the preoperative situation. At the 1 month interval, 6 patients (75%) experienced postoperative pain. After 12 months, this number had decreased to 1 patient reporting residual postoperative pain, scoring a 3 (out of 10) on the VAS. Six patients (75%) stated they would apply for surgery again in hindsight.

The next part of the evaluation consisted of the KHQ, which the patients completed at 4 specific points during follow-up (1, 3, 6 and 12 months postoperatively). After 1 month a significant improvement was observed in 3 of 10 subcategories, namely 'incontinence impact', 'physical limitations' and 'severity measures'. After 3 and 6 months the KHQ showed significant improvement in 4 of 10 (40%) and 5 of 10 (50%) of the subcategories, respectively. The only difference between the 3-month and the 6-month interval was the subcategory 'severity measures', which did not show improvement

after 3 months. At the end of 12 months, a significant improvement was seen in 6 of 10 (60%) subcategories, including 'incontinence impact', 'general health' and 'physical limitations' (table 2). The patient that had received an AUS 9 months postoperatively was excluded from the 12 -month follow-up.

Table 2 KHQ preoperative and 12-month scores

Domain	Mean	Std. Deviation	P[a]
General health			
Preoperatively	31.25	17.68	
12 Months	46.43	22.49	**0.008**
Incontinence impact			
Preoperatively	83.33	25.12	
12 Months	23.81	25.19	**0.023**
Role limitations			
Preoperatively	64.58	22.60	
12 Months	14.29	17.82	**0.008**
Physical limitations			
Preoperatively	54.17	29.21	
12 Months	9.52	8.91	**0.007**
Social limitations			
Preoperatively	38.89	31.57	
12 Months	4.76	12.59	0.050
Personal relationships			
Preoperatively	40.48	34.50	
12 Months	16.67	19.24	**0.037**
Emotions			
Preoperatively	41.67	27.05	
12 Months	7.94	13.93	0.059
Sleep/energy			
Preoperatively	31.62	37.81	
12 Months	14.29	14.99	0.386
Severity measures			
Preoperatively	50.35	15.25	
12 Months	21.03	11.55	**0.012**
Symptom severity			
Preoperatively	12.57	5.16	
12 Months	9.67	2.42	0.268

P <0.05 was considered statistically significant, a: paired two-tailed *t*-test

Discussion

The first part of this study identified 23 patients described in 6 previous studies that had undergone sling surgery for post-TURP SUI. The postoperative success rate was 78.3% (18 of 23 patients). The second part of this paper prospectively analysed the effects of the Virtue® male sling in 8 patients with post-TURP SUI. After 1 year, 4 of 8 patients did not require the use of pads and were considered cured. Another 2 patients had a pad reduction of over 50% and were considered improved.

To date, there are few studies that evaluate the results of the Virtue® male sling. The cure rates found in earlier studies are comparable to those found in the current cohort. In accordance with our results, Comiter et al. also experienced equal improvement rates for patients with mild, moderate and severe preoperative SUI. These findings are in contrast to papers on other slings that associate higher preoperative incontinence rates with lower postoperative continence rates (13-16).

In general, male slings appear to be less effective in the treatment of post-TURP SUI in comparison to SUI following a RP. Incontinence following a prostatectomy may be caused by either sphincter dysfunction or bladder dysfunction. Incontinence following a TURP is usually caused by damage to the proximal part of the (rhabdo) sphincter distal to the seminal colliculus (verumontanum) (5). However, the mechanisms for either trans-obturator or bone-anchored slings are not yet fully understood. In theory, trans-obturator slings such as the AdVance™ (American Medical Systems, Minnetonka, MN), function through relocation of the bulbar urethra in the pelvis, which then leads to angulation and lengthening of the membranous bulbar urethra (26). In contrast, a bone-anchored sling such as the InVance™ (American Medical Systems) is believed to achieve continence by exerting pressure on the bulbar urethra, resulting in an increase in outflow resistance (27).

The Virtue® male sling combines perineal urethral compression with proximal urethral relocation. Results of the current study show that, in contrast to other slings in current literature, the Virtue® male sling appears to be as effective in patients post TURP as in patients with a RP in their medical history. These findings support our hypothesis that the dual design of the Virtue® sling is more suited for post-TURP SUI than other conventional male slings that work through either compression or relocation of the urethra (13;14).

There are certain limitations to this study that need to be addressed. The first limitation is the fact that 3 out of the 6 (50%) selected articles included in our review did not differentiate between cure and improvement rates, which makes a comparison to our results more difficult. This lack in uniformity and the absence of a clear definition of success (and improvement) remains a problem when comparing different studies and techniques. Second, the clinical part of this study was performed in a single center

setting and included only 8 patients. Nevertheless, our review revealed that at present no studies describing a similar group of patients are known, making this study the largest cohort of its kind. Nevertheless, more extensive research, with larger cohorts and longer follow-up, should be performed before viable conclusions may be drawn.
In conclusion, little is currently known about the effects of sling surgery in patients suffering (mild to severe) SUI after a TURP. Although the Virtue® male sling seems to be an efficient and safe device in the treatment of this complication, long-term follow-up and larger cohorts are needed to further confirm these results.

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The somatic and autonomic innervation of the clitoris; preliminary evidence of sexual dysfunction after minimally invasive slings

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7

Introduction

Within a decade, the mid-urethral (vaginal) slings (MUS) became the most popular surgical treatment for stress urinary incontinence (SUI), with more than one million women treated (1). Despite the numerous studies on objective and subjective outcomes of this minimally invasive procedure, very few studies have addressed the impact of vaginal sling procedures on sexuality. Small series evaluating the sexual wellbeing before and after the tension-free vaginal tape (TVT), the in-out trans-obturator (tension-free vaginal tape-obturator (TVT-O)), and/or the out-in trans-obturator (trans-obturator tape (TOT)) procedures show conflicting results. Of these studies, some suggest deterioration (2-7) of sexual function, some improvement (2-4;8-11), whereas others were equivocal (12-16). A prognostic factor in the improvement of the sexual functioning of these patients is the cure of incontinence during intercourse (17;18). Negative effect on sexuality is hypothesized to be related to the implanted material because of the damage to important vascular and/or neural genital structures (2-7). Another interesting theory is that through movement of the clitoris during intercourse, incontinence tapes could also lead to an altered sexual function without initial nerve damage (19).

The clitoris plays an important role in achieving female orgasm by sexual stimuli (20). It is innervated by the dorsal nerves of the clitoris (DNC). These peripheral sensory afferents of the clitoris originate from the pudendal nerve (PN). The clitoris is also innervated with fibers coming from the autonomic pelvic plexus (also known as the inferior hypogastric plexus (IHP)): the cavernous nerves of the clitoris (CN). Clitoral and labial swelling during sexual arousal is associated with parasympathetic vasodilator mechanisms, among which nitric oxide (NO) appears to be a primary neurotransmitter contributing to the mediation of this function (21-23). NO control of vasodilatation and neuronal signalling between the cavernous nerves and the DNC contribute to the engorgement and subsidence of clitoral tissue. This supports the initiation of sexual arousal by tactile stimuli of the clitoris (24;25). Therefore, in theory, injury to the clitoris and/or its innervation, both somatic and autonomic, could lead to altered sexual function.

To investigate the anatomical relation of vaginal slings to important neurogenital structures, basic knowledge about and detailed descriptions of the neuroanatomy of the clitoris are needed. Research has demonstrated the integral relationship between the clitoris, distal urethra, and vagina (23;26-28). O'Connell et al. provided a major contribution to the research on the anatomy of the clitoris (26;29). They found the erectile tissue of the clitoris to be intimately related to the distal urethra, which leads them to suggest a role of the urethra in sexual function (26). The DNC was described in detail; the autonomic nerves, however, were poorly addressed.

In the research conducted by Moszkowicz et al. (23), the autonomic neural pathway as well as the DNC were described in detail in female fetuses. Although this research

did not link its results directly to medical practice, it is still very illustrative for a deeper understanding of the clitoral neural anatomy.
Disruption of the somatic innervation of the clitoris can lead to a diminished sensibility of the clitoris, thereby affecting sexual arousal due to the absence of tactile stimuli. The DNC is located along the medial aspect of the inferior pubic ramus (IPR) where it runs along the pubic bone in a sulcus; described as the sulcus nervi dorsalis clitoridis (30).
Risk of injury to the DNC along the IPR has been suggested by Delorme with the medial to lateral passage of the needle which is used for placing vaginal slings. This injury could then alter postoperative sexual function such as arousal, orgasmic function, or pain (31). This possible risk has been illustrated by Lowenstein, showing the topographic relation of MUS for SUI to critical female genital structures (32). In a cadaveric study, performed by Achtari et al., the potential risks of three vaginal slings to the DNC were evaluated. Distances of a TVT, in-out trans-obturator (TVT-O), and out-in trans-obturator (Monarc) to the DNC were similar (11–12 mm) (33). Given the outside-inside course, the Monarc was claimed to (theoretically) be the safest device. Another cadaveric study found similar results, although they only documented the course of the DNC from the piercing of the perineal membrane to its terminal branching and not its course along the IPR (34).
The CN are involved in the neural control of vasocongestion and, consequently, the lubrication swelling response. Disruption of these nerves could lead to altered vascular function during sexual arousal and possibly disordered orgasm. However, although important for normal sexual function, in aforementioned studies, no attention was paid to the possible effects of disruption of the CN (23;32-34).
The aim of this study was to reinvestigate the neuroanatomy of the clitoris by performing dissection in 14 adult female hemipelves and by using (immuno)histochemical and three-dimensional (3-D) reconstruction techniques on sectioned female fetuses. In this study, we focus on: (i) the autonomic innervation of the clitoris; (ii) the course of the DNC; and (iii) the investigation of the anatomical sites of potential nerve damage during vaginal sling surgery for SUI.

Methods

Fetal 3-D Reconstruction

Fetal pelves from the collections in the departments of Anatomy and Embryology at the Leiden University Medical Center and at the Amsterdam Medical Center were studied. Eleven paraffin-embedded fetuses (all female), ranging from 10 to 27 weeks of gestation, 6–26 mm crown-rump length, were serially sectioned. Six were stained with hematoxylin and eosin, three with hematoxylin-azophloxine, and two with both hematoxylin and neurofilament (35). The fetal tissue was fixed in 4% paraformaldehyde embedded in paraffin,

and transversely sectioned into serial sections of 10 mm. Analysis of the transverse sections was performed from the superior part of the pubic arch to just below Alcock's canal. Digital images were taken from the serial sections, photographing every second section. These images were used to prepare 3-D reconstructions with the Amira software package (v3.0, Visage Imaging GmbH, Fürth, Germany). The perineal membrane (or urogenital diaphragm) was not detectable in these fetal series and therefore not reconstructed.

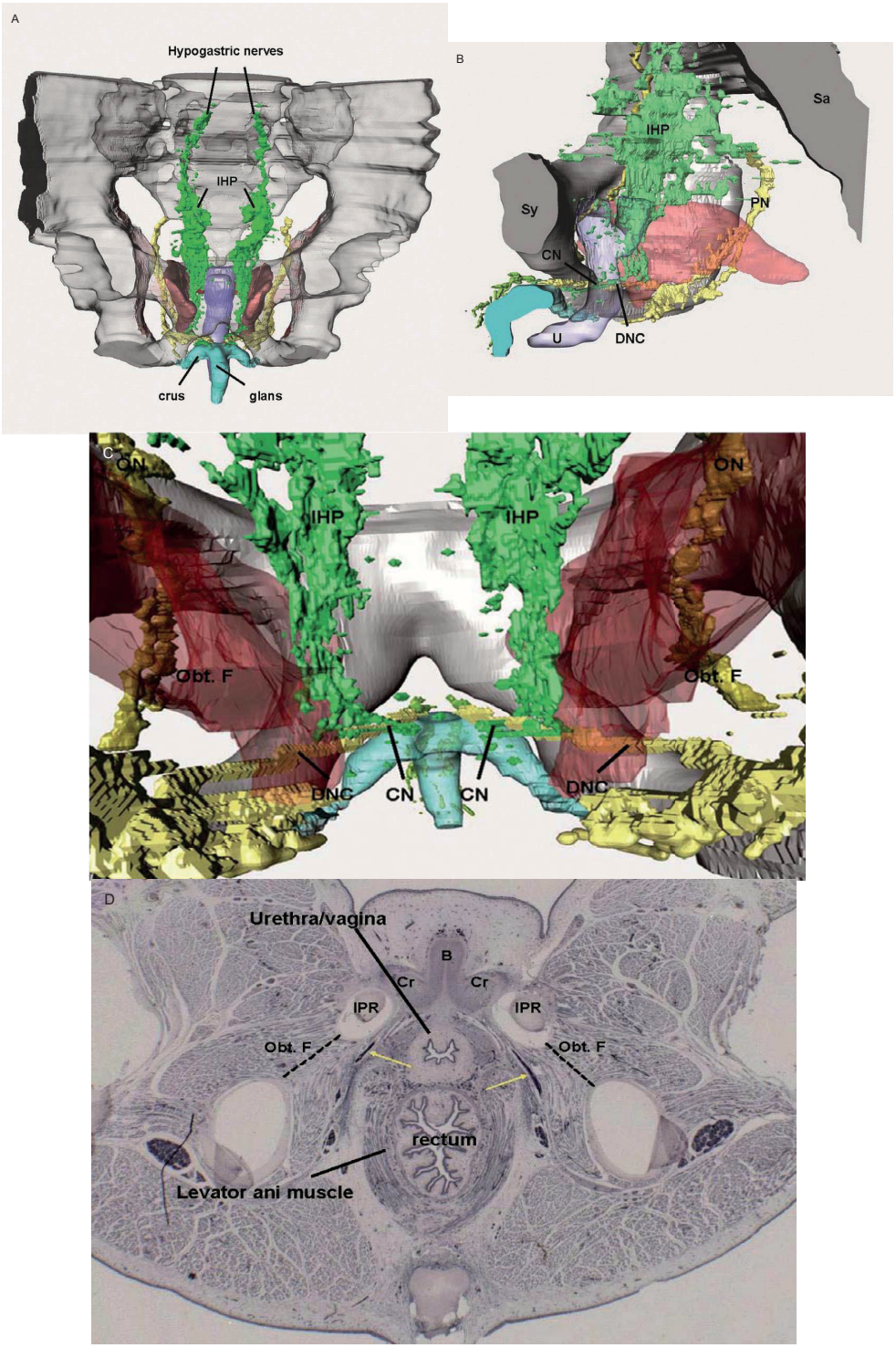
Cadaver Study

The pelves of female cadavers without signs of any pelvic surgery were used for this study. Usually, the age of death of these women is over 70 years of age. Preservation of all used bodies was performed by injection of AnubiFIX™ into the femoral artery followed by the embalming fluid, consisting of 36% formaldehyde with a mixture of ethanol, glycerin, phenol, K2SO4, Na 2SO4, NaHCO3, NaNO3,andNa2SO3. Due to this fixation process, the pelvic structures remained flexible which enabled natural dissection and allowed surgical procedures. The cadavers were donated to the university for medical research and, hence, did not require separate ethics approval for dissection. A trained urologist (HWE) performed both procedures (TVT and TVT-O) on the first cadaver, one on each side. After this test, three more TVT-O, and three more TVT procedures were performed on the female cadavers. All procedures were performed exactly similar as they would have been on normal patients.
The pelves were sectioned through the midline from the pubic symphysis anteriorly to the sacrum posteriorly. The urethra was sectioned along its full length in the midline. The clitoris and its somatic and autonomic nerves were dissected, and the shortest distance between the sling and the nerves was documented. All the stages of the dissection were recorded photographically. One hemipelvis with a TVT placed could not be properly dissected due to a large hematoma and was therefore excluded.

Results

Anatomy of the Clitoris

The clitoris is a multiplanar structure medial inferior to the pubic arch and symphysis. It is positioned deep to the labia minora, labial fat and vasculature, the musculus bulbospongiosus, and the musculus ischiocavernosus. It has a broad attachment to the pubic arch, and via extensive supporting tissue to the mons pubis (the adipose tissue lying above the pubic bone of adult females, anterior to the pubic symphysis) and labia. The clitoris consists of a tip, also known as the glans of the clitoris, the erectile body, and the crura (or corpora cavernosa) (Figure 1A). The clitoris has a close relationship to the distal urethra and vagina (Figure 1B). Because this study involved human fetuses, aged 10–27 weeks of gestation, these two structures are still partly merged.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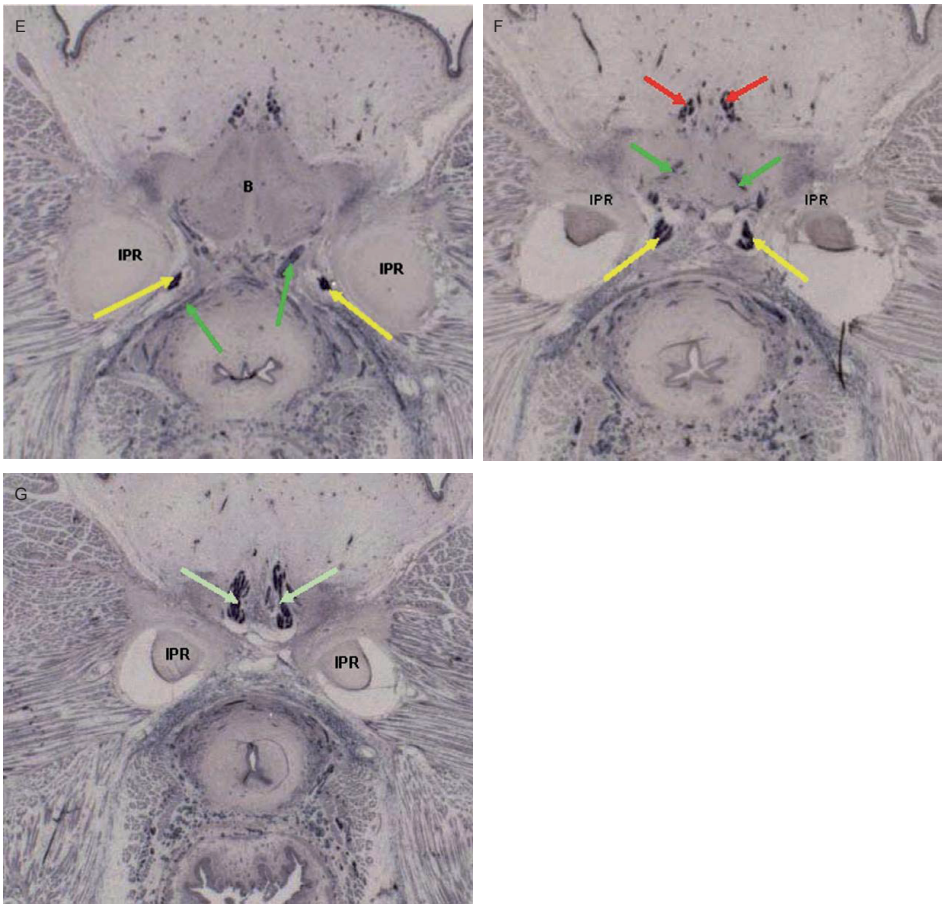


Figure 1 (A) Anterior view (3D) of the clitoris (blue), the pelvis (grey), the pudendal nerves (yellow), the hypogastric (autonomic) nerves (green) traveling into the pelvis and forming the inferior hypogastric plexus (IHP), and the merged autonomic and dorsal nerves (light green). (B) Lateral view (3D) of the midsaggital cut pelvis with the symphysis (Sy) centered (grey) the levator ani muscle (red), the clitoris (blue), the autonomic (green) and somatic (yellow) nerves, and the distal urethra/vagina (U, purple). (C) Anterior and slightly lateral view (3D) of the pelvis (grey) the obturator foramen (Obt. F), the obturator nerve (ON), the clitoris (purple), the dorsal nerve of the clitoris (DNC, yellow), and the cavernous nerves (green, CN) coming from the IHP. (D) Stained section showing the body of the clitoris (B) with its crura (Cr) close to the inferior ramus of the pubic bone (IPR), and the dorsal clitoral nerves (yellow arrows) passing along the Obt. F. (E) Stained section, the close relationship of the IPR to the clitoral dorsal nerve (yellow arrows), is notable and it shows that the branches of the cavernous nerves of the clitoris pass medial to the dorsal nerves (green arrows). (F) Stained section, showing both cavernous nerves (green arrows) and the dorsal nerves of the clitoris (yellow arrows) hooking over the clitoral body and traveling further caudally alongside and into the clitoral body and glans (red arrows). (G) Stained section, the autonomic nerves merge with the branches of the dorsal nerves as they pass over the clitoral body (light green arrows). B = clitoral body; PN = pudendal nerve; CN = cavernous nerve; Sa = sacrum

DNC

The 3-D reconstruction illustrates the course of the dorsal clitoral nerves. They originate from the PN in the Alcock's canal immediately medial to the pubic bone and lateral to the rectum, forming a bundle that fans out laterally, passing the levator ani muscle and ascending to the clitoral bodies (Figure 1A–C). The 3-D images also revealed that both DNC run medial and close to the ischiopubic ramus (Figure 1C). Furthermore, the close relationship of the clitoral crura to the clitoral dorsal nerve was notable. They traverse distally alongside the clitoral crura and run posterior to the body of the small pelvis, to be joined by the pelvic splanchnic nerves coming from sacral roots S2 to S4, to form the pelvic plexus, also known as the IHP on both sides of pelvic organs (Figure 1A). The IHP showed to be a triangularly shaped plexus in a sagittal plane. It is in close contact with its target organs as a flat meshed plaque of nerve tissue, stretching from anterolateral to the rectum, passing the cervix and vagina laterally, and extending from the lateral vaginal wall, to the base of the bladder and lateral to the urethra with branches to the clitoris.

The branches extend onto the lateral walls of the proximal and mid-vagina, where they form a dense network. These nerves travel superior to cover the proximal anterior vaginal wall, where they form the cavernous nerves at the 2 and 10 o'clock positions alongside the urethra (Figure 1C, E). There, they travel further caudal to the clitoral bodies crossing the dorsal clitoral nerve medially. The nerve bundles then travel alongside the branches of the dorsal nerve passing over the clitoral body. After passing over the clitoral body, these autonomic nerves merge with the branches of the dorsal nerve and travel further caudally alongside and into the clitoral body and glans (Figure 1B, F, G).

Dissection

Anatomy of the Clitoris

The initially almost straight clitoral crura run proximally along the ischiopubic ramus and join distally under the pubic symphysis as a single clitoral body that projects anteriorly into the glans and the fat of the mons pubis. Dissection shows that the apex of this triangular structure is the most superior point of the clitoral body, where it attaches to the under surface of the pubic symphysis by the deep suspensory ligament (Figure 2). As the clitoral body projects from the bone into the mons pubic fat, it descends and folds back on itself in a boomerang-like shape in a dorsal caudal direction forming the glans of the clitoris. The glans of the clitoris is a relatively small nodular structure that becomes partially covered by the glandopreputial lamella and prepuce (or clitoral hood).

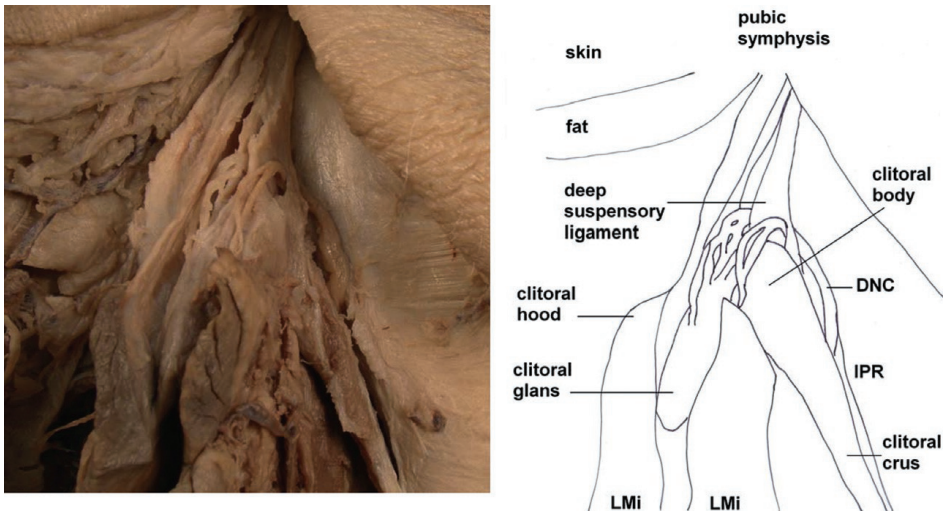


Figure 2 Anterior view of the dissection clitoris. The mons pubis has been opened to show the deep suspensory ligament. Furthermore, the clitoral crus, body, and glans are shown with the dorsal nerve of the clitoris (DNC) ascending along the inferior ramus of the pubic bone (IPR), hooking over the clitoral body while passing through the suspensor ligament and branching into the clitoris. LMi = labia minora

DNC

The course of the PN around the ischial spine was approached posteriorly by removal of the skin and superficial fascia between the anterior inferior iliac spine, the ischial tuberosity, and the posterior superior iliac spine. The gluteus maximus muscle was dissected from its origin to expose underlying structures. The sacrotuberous ligament was identified and transected to identify the PN subjacent to the sacrotuberous ligament and around the ischial spine of the pelvis. The entrance of PN into Alcock's canal was identified. Alcock's canal was then unroofed which revealed the three main branches of the PN, namely the inferior rectal nerve, the perineal nerve, and the DNC. The DNC was then followed until its termination in the clitoris. The DNC travels along the perineal membrane (or urogenital diaphragm) and runs inferiorly to the inferior pubic ramus (IPR). By opening the perineal membrane, the TVT-O tape was exposed (Figure 3A, B). The distance of the TVT-O to the DNC is shown in Table 1and has a mean of 9 mm. It is further important to report that the TVT-O and the DNC were separated by the perineal membrane in all pelves. See Figure 3C for a schematic overview of the DNC in relation to the TVT-O.

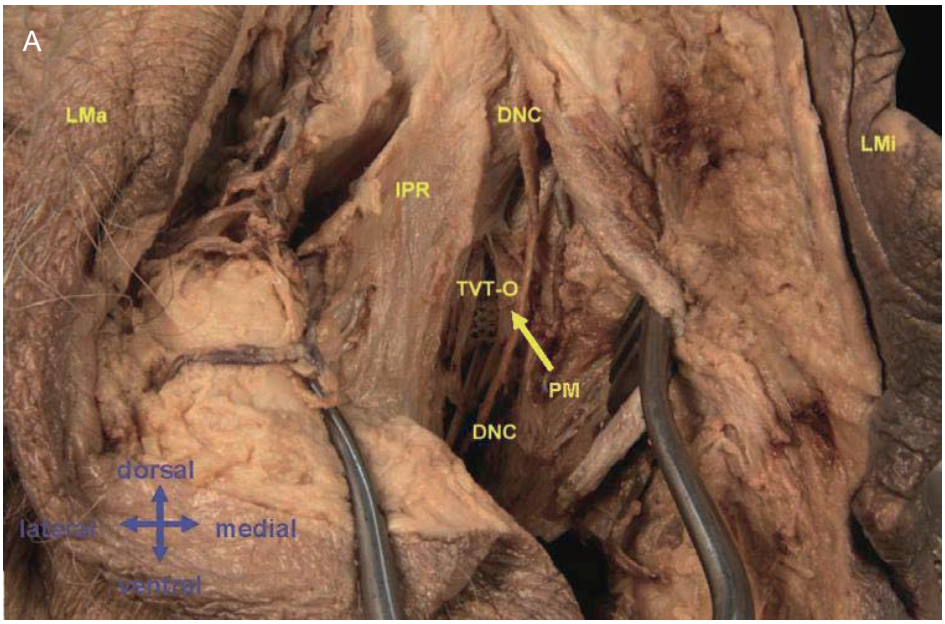
Table 1 Distance between the TVT, TVT-O, and the clitoral nerves

Distance to tape (mm)*	**Cadaver 1‡**		**Cadaver 2**		**Cadaver 3**		**Cadaver 4**	
Dorsal nerve of clitoris	L	R	L	R	L	R	L	R
TVT-O Mean: 9 mm	—	6	12	19	9	6	6	5
Distance to tape (mm)†	Cadaver 1‡		Cadaver 5§		Cadaver 6		Cadaver 7	
Cavernous nerves	L	R	L	R	L	R	L	R
TVT	0	—	—	0	0	0	0	0

*Distance from dorsal nerve of clitoris
†Distance from cavernous nerves of clitoris
‡Left TVT, Right TVT-O
§Left side excluded due to hematoma

Autonomic Nerves

The superior hypogastric plexus was identified inferiorly to the bifurcation of the aorta in all pelves. The proximal hypogastric nerves were identified in the subperitoneal layer (between the peritoneum and the endopelvic fascia) and followed alongside the ureter into the small pelvis to the IHP. Figure 4 is a lateral view of a midsagittal sectioned right pelvis showing the course of the autonomic nerves from the hypogastric nerve to the target organs. The IHP is a flat meshed plaque of nerves. Its branches, which follow the connective tissue plane within the small pelvis that supports the uterine cervix, vagina, and bladder, were identified and dissected into their target organs. Special attention was paid to the branches passing alongside the urethra and innervating the clitoris. The autonomic nerves, running from the IHP, were found to be pierced by the TVT needle in all pelves (Figure 4). See Figure 4C for a schematic overview of the autonomic nerves in relation to the TVT.



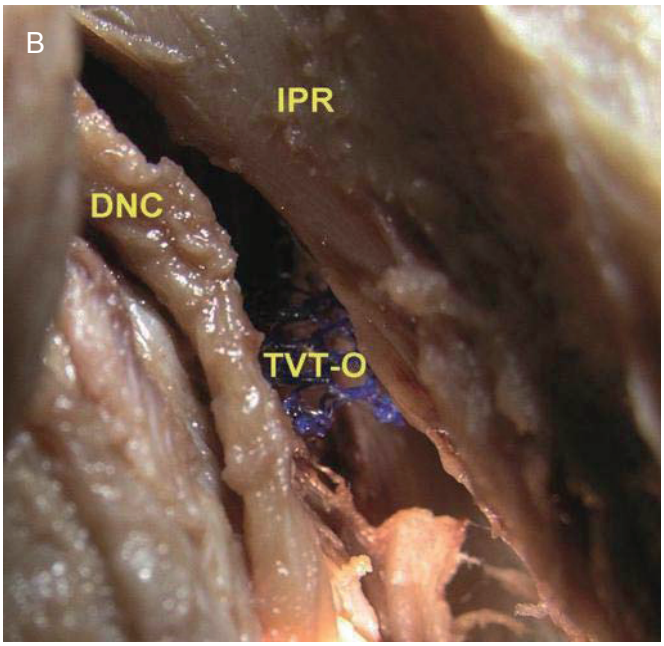
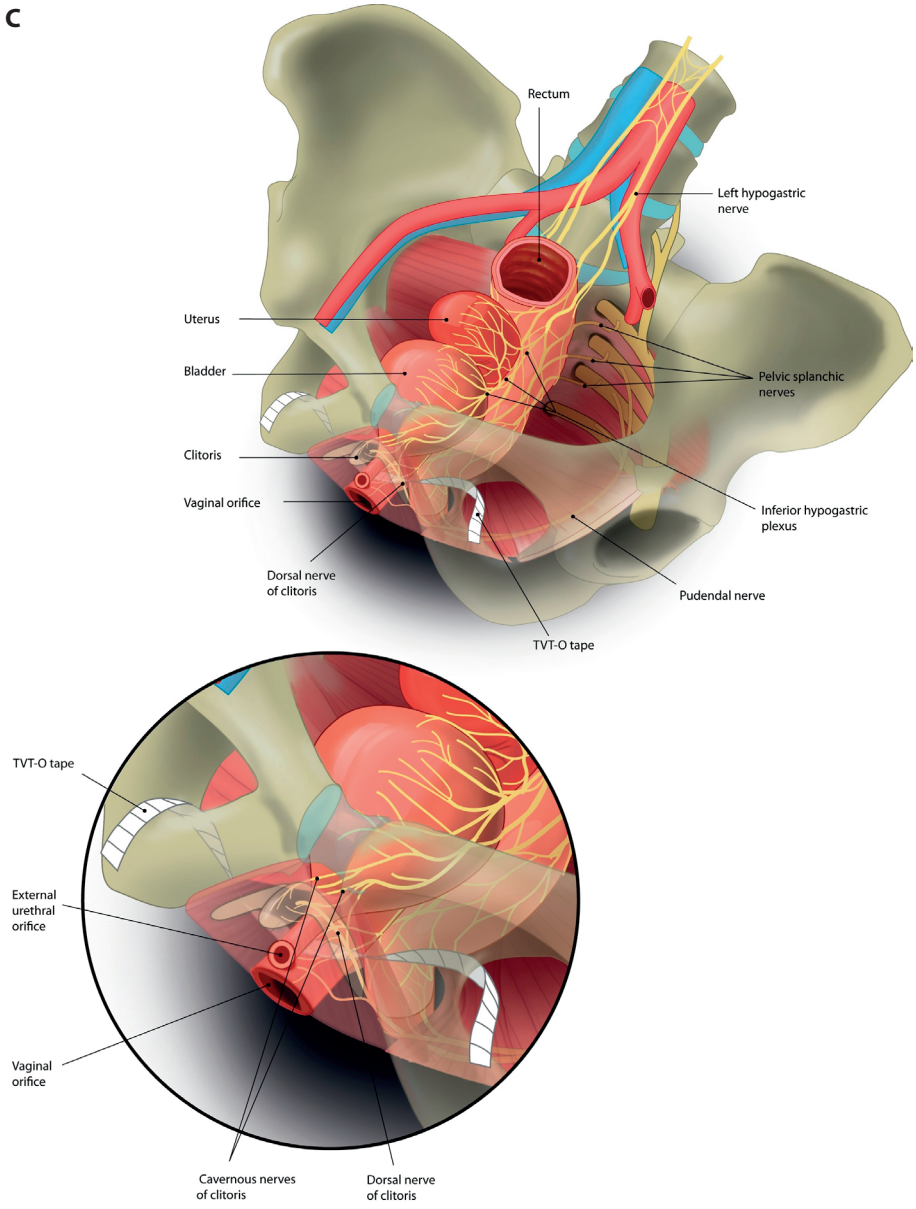


Figure 3

(A) Frontal view of the right female genital and perineal area. In order to expose the dorsal nerve of the clitoris (DNC), the skin was opened between the right labia majora and minora. To show the route of the tension-free vaginal tape-obturator (TVT-O) sling, the perineal membrane was opened subsequently. (B) Close-up of TVT-O and DNC. IPR = inferior pubic ramus; LMa = labia majora; LMi =labia minora; PM = perineal membrane.



(C) Relation between the DNC and the TVT-O.

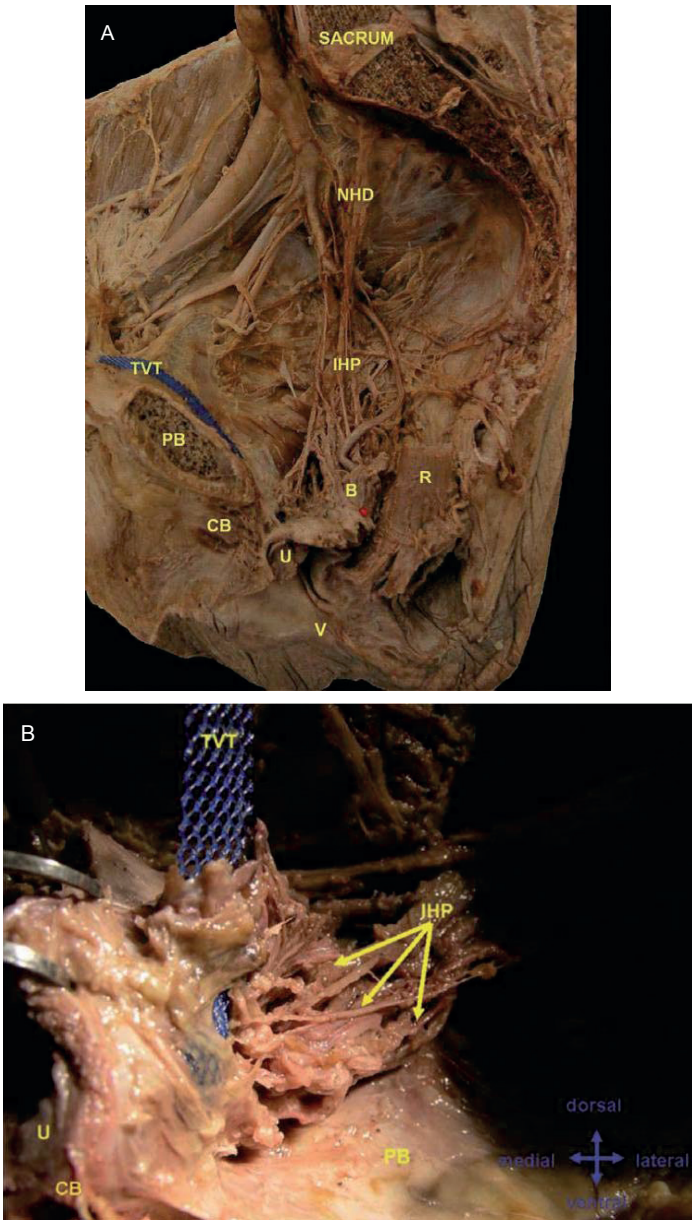


Figure 4 (A) Lateral view of a midsagittal-sectioned right pelvis showing the course of the autonomic nerves originating from the nervus hypogastricus dexter (NHD) through the inferior hypogastric plexus (IHP) to the clitoral body (CB) and the urethra (U). The uterus as well as the largest part of the bladder (B) were removed in order to get a clearer view of the course of the autonomic nerves. (B) The final branches of the IHP (close up). The dissected urethra (U) and surrounding tissue are withdrawn from the pubic bone (PB) to expose the final nerve branches originating from the IHP and finally reaching the urethra and CB. As seen the TVT pierces these cavernous nerves. PB = pubic bone; R = rectum; V = vagina

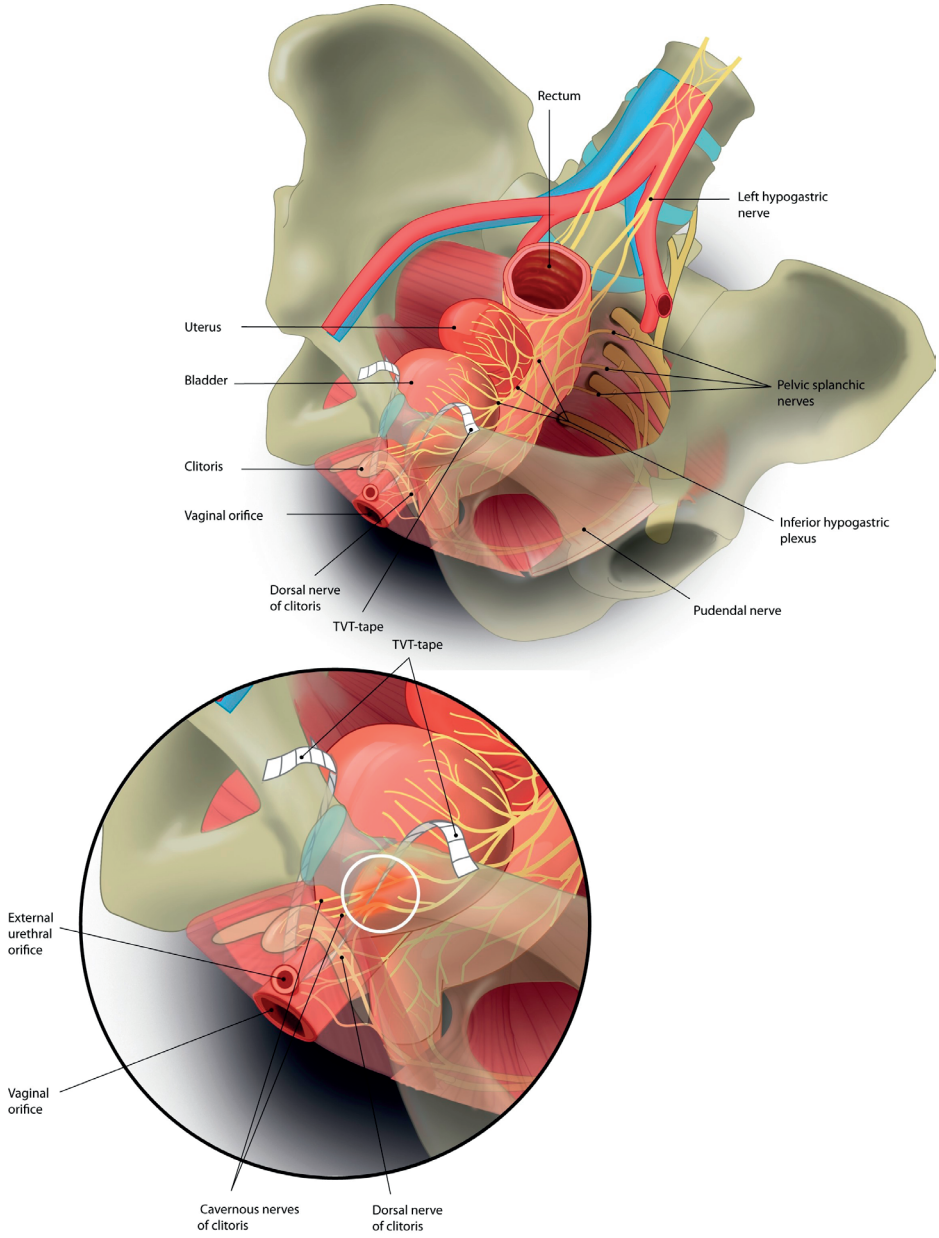


Figure 4 (C) The relation between the autonomic nerves and the TVT.

Discussion

This study describes the somatic and autonomic anatomy of the clitoris. Most of the previous studies on the innervation of the clitoris were mainly focused on the DNC, paying no attention to the cavernous nerves coming from the pelvic plexus, which play an important role in female sexual function (26;28-30;34;36-38). The cavernous nerves are involved in the neural control of vasocongestion and, consequently, in the lubrication-swelling response and were described by Moszkowicz et al. (23).

Disruption of these nerves could lead to altered vascular function during sexual arousal and possibly disordered orgasm. In 1982, Walsh and Donker described the anatomic location of the pelvic plexus (or IHP) in men and the nerves innervating the corpora cavernosa (39). These pioneering observations and descriptions of the anatomical basis for radical prostatectomy fostered resurgence of surgery as treatment for localized prostate cancer and led urologic surgeons to refine a nerve-sparing technique within the following two decades. Only in the recent years, attention is paid to the IHP in females and nerve-sparing techniques are being developed in surgery for cervical cancer (40-42). Although the IHP has been described in females, little attention has been paid to the cavernous nerves coming from the IHP and their anatomical relation to other pelvic structures (29). Yucel et al. and Moszkowicz et al. both reported that the cavernous nerves supply the female urethral sphincter complex and clitoris (23;28). The branches of the cavernous nerves were described and, as in our study, noted to join the clitoral dorsal nerves. The cavernous nerves have also been described in mice and guinea pigs, using immunostaining to show communicating nerves between the cavernous nerve and the DNC which supports the initiation of sexual arousal by tactile stimuli and following clitoral swelling (24;25). This study underlines the importance of both somatic and autonomic innervation of the clitoris in normal female sexual function.

Vaginal sling procedures for SUI have been developed in the 1990s by Ulmsten et al. (43). After research, the procedure showed to be safe and effective, and the TVT and derived procedures became well-established surgical procedures for the treatment of female SUI. Especially in these early years, no attention was paid to the topographic relation to important genital structures. Only in recent years, the possible risk of nerve damage during vaginal sling procedures, especially the obturator procedures, has been suggested (32).

The aim of this study was to describe not only the neuroanatomy of the clitoris but also its relation to surrounding structures which are anatomical landmarks in vaginal tape procedures for SUI.

When performing vaginal sling surgery, a sagittal incision is made within the anterior vaginal wall mucosa about 1 cm from the urethral meatus and the vaginal wall is dis-

sected from the mid-urethra. When performing the TVT procedure, a tape is placed (blindly) behind the pubic symphysis using trocars attached to the tape (43).
When performing the TOT, the "outside-in," procedure, a similar midline incision is made in the anterior vaginal wall between the mid-urethra and bladder neck. Dissection is carried out laterally to the level of the vaginal sulcus without penetration of endopelvic fascia. The IPR and the obturator foramen are located manually, and the medial edge of the ramus is pinched between the thumb and index finger. The skin puncture is made at the level of the clitoris right above the pinching thumb. The curved sling passer is guided from the thumb to the index finger, and then rotated and delivered to the vaginal incision with the tip on the index finger. The arm of the tape is hooked to the tip of the passer and brought out to the skin (31). When performing the TVT-O (inside-out), a similar midline incision is made and periurethral tunnels are developed bilaterally. Unlike the TOT, where the dissection stops at the IPR, with the TVT-O, the obturator membrane is perforated with the tip of the scissors. A winged metal trocar, which is designed to help guide the tape around the IPR, is inserted into the periurethral tunnel and the tip is pushed just beyond the perforated membrane. The trocar is then rotated around the IPR to exit out via the skin through stab incisions located 2 cm above a horizontal line at the level of the urethral meatus and 2 cm outside the thigh folds. The same procedure is performed on the other side, the sling is tensioned, and the procedure completed (44). As described, during these procedures, the part of the mid-urethra along the anterior vaginal wall is an important surgical site; here, the first incision is made. This study illustrates that the urethra is surrounded by autonomic nerves coming from the IHP. Not only do they travel to and innervate the urethra, the cavernous nerves travel from the vaginal nervous plexus occupying the 2 and 10 o'clock positions on the anterolateral vagina, and they travel at the 5 and 7 o'clock positions alongside the urethra. It is therefore possible that during the mid-urethral incision in all vaginal procedures and the para-urethral tunneling during the obturator procedures, the cavernous nerves are disrupted. The cadaveric part of this study showed that the cavernous nerves were indeed pierced during the TVT procedure. These results are further confirmed by the pilot study by Caruso et al. in 2007 (45) in which the clitoral blood flow significantly decreased after the TVT procedure. These findings further support our conclusion that the TVT procedure causes iatrogenic damage to the CN.
The IPR plays an important role in the obturator procedures; the tapes are placed around this bony structure. Furthermore, dissection is performed para-urethral to the IPR, and during the inside-out technique, the obturator membrane is perforated with scissors. Because the DNC travels along the medial side of the IPR, it could potentially be damaged during obturator procedures, both outside-in and inside-out. The results of the dissections did not confirm this, although the distance between the tape and the DNC was only 9 mm. Achtari et al. also dissected female cadavers and measured

the distance of the DNC to the TVT, TVT-O, and Monarc. Their results showed a distance varying from 19 mm to 40 mm, the TVT-O being the closest to the DNC (33). A similar study in fresh cadavers measured a distance between the DNC and the TOT of 3–14 mm. Despite this small distance, they concluded the TOT to be a safe procedure. This last study was however biased because straight needles were used to mimic the course of the TOT, instead of curving trocars (34). Our study showed a median distance of 9 mm. from the TVT-O to the DNC. The results found in dissection, in combination with the fetal anatomy, could indicate that when dissecting in the direction of the foramen, the DNC is potentially at risk for injury.

This study is one of the first to illustrate, in detail, both the somatic and autonomic pathways of the clitoris and link these results directly to medical practice. Significant progress has been made in the field of female sexual anatomy and its representation. This study facilitates further research in related fields of female sexual health and education, and can be used by surgeons in the field of urogynecology. Furthermore, the topographic relation of vaginal slings to the important critical female genital structure, the clitoris, has been illustrated and described for the first time. Limitations of this study were the unevaluated role of clitoral movement during intercourse (19) and post-surgery tissue reaction (fibrosis of the tape) (46). Future (clinical) research should be performed to confirm these results and to determine the consequences of injury to the clitoral nerves on the clitoral sexual response and female sexual functioning.

Conclusion

The DNC is located inferiorly to the pubic ramus and was in this research not disturbed during the placement of the TVT-O. However, the autonomic innervation of the vaginal wall and clitoris was disrupted by the TVT procedure. It is also shown that when the "inside–out" technique is used, the introducer could hypothetically come into contact with the DNC, although this did not show in our results. Summarizing, this study illustrates that the retropubic technique clearly disrupts the nervous system to the clitoris and that the obturator technique does not. Further evidence will be needed from clinical studies to decide which technique should be recommended for which patient, in order to achieve the highest possible quality of life.

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Risk of damage to the somatic innervation of the penis during the AdVance™ procedure: an anatomical study

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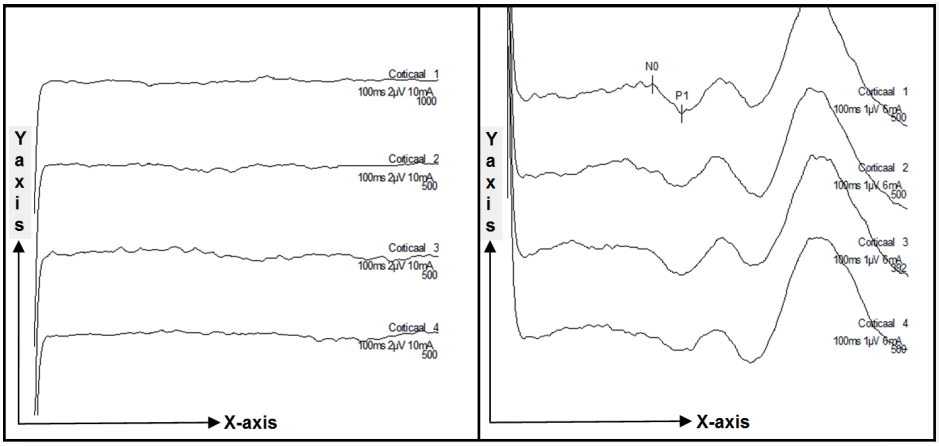
8

Case

A total of 32 AdVance™ male slings have been placed between 2007 and 2011 at the Leiden University Medical Center in patients suffering from SUI after a nerve sparing RP. Directly following an otherwise uncomplicated procedure, one patient complained of de-novo anesthesia of the right side of the penis. Since the anesthesia occurred directly post-surgery it could only be explained by neurological damage suffered during the placement of the sling. In the following period the sensory nerves of his penis were analysed using Somato Sensory Evoked Potentials (SSEP's), in order to identify the origin of the anesthesia. SSEP's are based on the electrical stimulation and response of individual somatic nerves that are reproduced as cortical curves with the SSEP's showing as evident peaks. The subsequent analysis showed complete interruption or neurotmesis of the right dorsal nerve of the penis (DNP), demonstrated by the lack of any response upon stimulation (figure).



Somatosensory evoked potential measurement of penis patient X
P: positive peaks represented by downward deflections, N: negative peaks represented by upward deflections. X-axis: time in milliseconds (ms), Y-axis: amplitude in in microvolts (µV).

The next chapter describes the anatomical relation between the AdVance™ male sling and penile nerves based on the dissection of 6 adult male pelves and investigating the sites of potential nerve damage during sling placement.

Introduction

One of the most popular treatment options for prostate cancer is the radical prostatectomy (RP). The two major complications following a RP are stress urinary incontinence (SUI) and erectile dysfunction (1). The post-RP SUI rates show a huge range throughout literature, but incontinence rates as high as 87% have been reported in the past (2). This divergence of reported SUI rates can be explained by the use of different surgical techniques as well as different definitions of continence. Despite an evolution in surgical techniques for RP following the introduction of (robot-assisted) laparoscopic prostatectomy over the past years, recently reported postoperative SUI rates are still between 5% and 48% (3). Moreover, the ever-growing number of radical prostatectomies worldwide entails increasing numbers of patients suffering postoperative SUI.

SUI due to sphincter incompetence is the most observed type of post-RP incontinence and initial therapy consists of lifestyle interventions, scheduled voiding and pelvic floor muscle training. After initial treatment has failed, invasive therapy should be considered. The recommended invasive treatment options for SUI due to sphincter incompetence are the placement of an artificial urinary sphincter or male sling (4).

The somatic peripheral nervous system is responsible for carrying motor and sensory information from (efferent) and to (afferent) the central nervous system. Standard anatomical literature shows that the somatic sensory information of the external male genital area is conducted to the sacral cord through the pudendal nerve (PN). The PN originates from sacral spinal segments 2–4 and travels through the Alcock's canal into the perineum. The PN has three major branches, namely the inferior rectal nerve, the perineal nerve, and the dorsal nerve of the penis (DNP). The DNP is the final branch of the PN and is considered the main somatic afferent nerve of the penis. It is responsible for the transfer of sensory input from the penis to the central nervous system and crucial for both erection and ejaculation (5). Damage to the DNP results in paresthesia or anesthesia of the innervated area and is highly invalidating in sexually active men (6;7).

The AdVance™ (American Medical Systems®, Minnetonka, MN, USA) male sling is a minimally invasive technique developed for the treatment of mild to moderate post-prostatectomy SUI. The AdVance™ repositions the urethral sphincter complex in the pelvis and is designed to minimize the risk of tissue damage during placement (8). In the initial study on the AdVance™, Rehder and Gozzi describe the anatomical effects of sling placement as well as the clinical outcome in men with SUI (8). In the results section, the authors state that "the penile vessels and nerves that lay in the 'shadow' of the inferior pubic ramus (IPR) were not injured by rotating the helical introducer needles" ((8) p. 863). Although the authors did not literally call the DNP by its name, it can be assumed that these were indeed the penile nerves described. The trajectory of the sling in relation to the pelvic neuro-anatomy was not pursued any further.

Following a complication in our clinic, in which the AdVance™ procedure resulted in a unilateral neurotmesis of the DNP, a literature search was performed via PubMed (using MeSH terms "neuroanatomy," "pudendal nerve," and "suburethral sling") to identify publications on the AdVance™. In this search, it became evident that there have been no studies up to present that analyse the trajectory and positioning of the AdVance™ in relation to the pelvic neuro-anatomy.

Aim

This study aimed to describe the anatomical relation between the AdVance™ male sling and penile nerves based on the dissection of 6 adult male pelves.

Methods

A total of 6 male donated Caucasian bodies from the Netherlands were used in this study. Bodies displaying any sign of surgery in the pelvic region were excluded. Preservation of the bodies was accomplished by injection of AnubiFIX™ (AnubiFIX, Gouda, the Netherlands) into the femoral artery followed by the embalming fluid, consisting of 36% formaldehyde with a mixture of ethanol, glycerin, phenol, K2SO4, Na 2SO4, NaHCO3, NaNO3, and Na2SO3. This particular fixation process ensures the flexibility of the pelvic structures such as muscles, nerves, arteries, and veins, and enables a realistic surgical procedure by retaining "lifelike" suppleness of the body. The bodies were all aged 70 years or older at the time of death and were donated according to the Dutch Burial and Cremation Act to the Department of Anatomy and Embryology at the Leiden University Medical Center for use in scientific research and medical education. As the bodies had been donated for medical research, no additional ethics approval was needed.

The procedures were conducted by the same urologist (HWE) who has extensive experience with the AdVance™ male sling and is experienced in placing mid-urethral slings in female cadavers for clinical research. The slings were placed using the same method and materials described by Rehder and Gozzi (8). After placement, the correct position of the mesh on the bulbar urethra was ascertained and the sling was fixated to the corpus spongiosum using two nonabsorbable sutures. The sling was then tensioned by pulling both arms of the sling, repositioning the urethral bulb.

After sling placement, the pelves were separated from the bodies, leaving the pelvic organs in place. First, the cutis and subcutaneous fat were removed from the dorsal side of the pelves, and the various muscle groups and cutaneous nerves were identified. Next, the consecutive tissue layers were dissected from the dorsolateral side of the pelvis, working in a ventral direction. After removal of the gluteal muscles, the ischial tuberosities were used as anatomical landmark to identify the ischial and PNs.

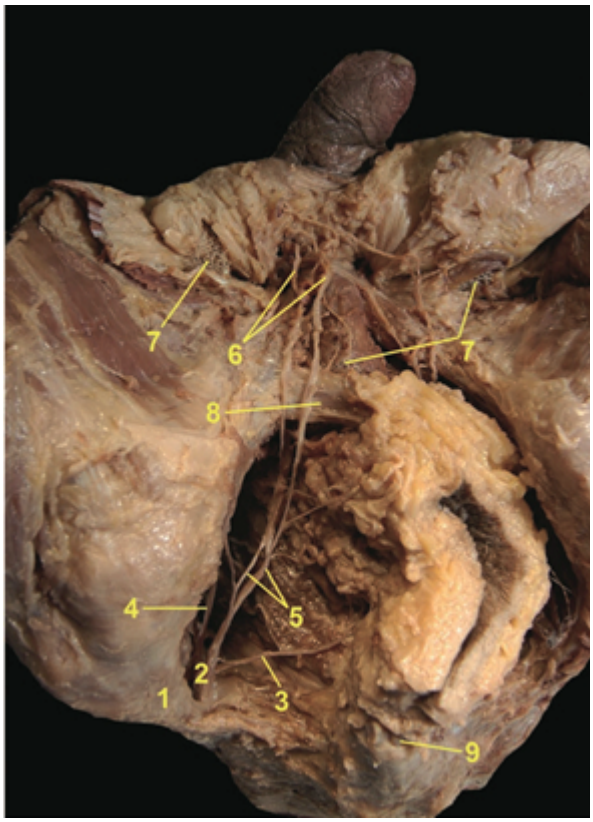


Figure 1 Course of pudendal nerve through the male pelvis. 1, sacrotuberous ligament; 2, pudendal nerve; 3, inferior rectal nerve; 4, dorsal nerve of penis; 5, perineal nerves; 6, posterior scrotal nerves; 7, AdVance™; 8, transverse perineal muscle; 9, coccyx

The PN arises from the sacral spinal segments 2–4 and travels though the Alcock's canal before entering the perineum. The course of the PN around the ischial spine was approached posteriorly by removal of the superficial fascia between the anterior inferior iliac spine, the ischial tuberosity and the posterior superior iliac spine. The sacrotuberous ligament was identified and the trajectory of the PN subjacent to the sacrotuberous ligament around the ischial spine of the pelvis was uncovered. The entrance of the PN into Alcock's canal was identified and dissected to reveal the PN and its three main branches (Figure 1). The DNP was then followed all the way through the perineum to its termination at the base of the penis.

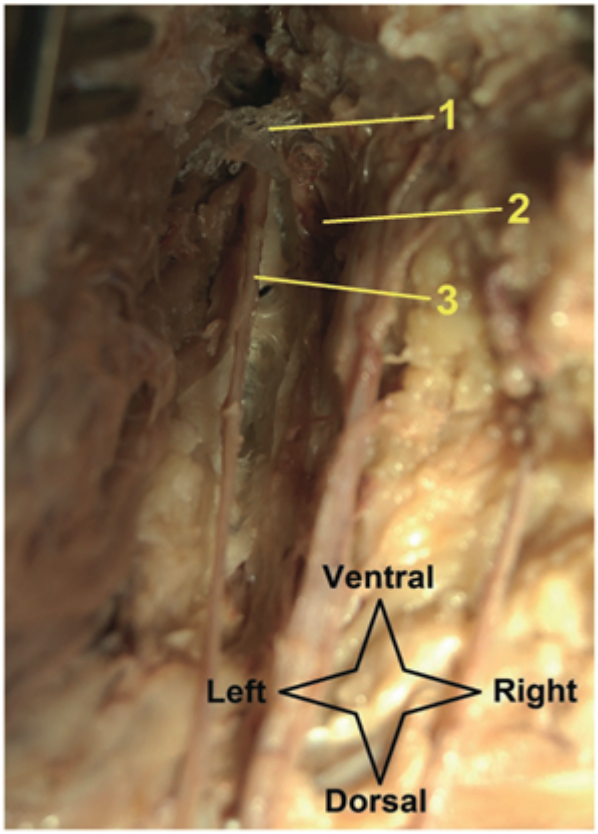


Figure 2 Close-up inferior view of the AdVance™ sling situated directly next to the dorsal nerve of the penis (DNP) in the right hemipelvis. 1, AdVance™ sling; 2, inferior pubic ramus; 3, DNP

At this stage the AdVance™ sling and its trajectory through the obturator foramen were fully exposed by opening of the perineal membrane (Figures 1 and 2). Next the pelvis was turned and the obturator foramen was exposed by removal of the adductor muscles of the hip and the external obturator muscle. The AdVance™ sling and obturator vessels and nerves were identified and followed through the internal obturator muscle. Finally, the distance of the AdVance™ sling to the DNP and obturator vessels and nerves was measured in all pelves. All stages of the dissection were recorded photographically using a high resolution digital camera with additional macro lens (Nikon™ D70, Nikon Corporation, Tokyo, Japan). Statistical analysis was performed using SPSS release 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Outcomes were considered statistically significant at the 95% level.

Main Outcome Measures

The main outcome measures werethe distance between the AdVance™ male sling, the DNP and the obturator neurovascular bundle.

Results

In all pelves, the DNP was found running in between the superior and inferior borders of the perineal membrane (or urogenital diaphragm), medial to the inferior border of the IPR, without signs of an aberrant course. The mean distance of the sling to the DNP was 4.1 mm and found situated directly next to the DNP (distance: 0 mm) in 4 out of the 12 hemipelves (33%, Table 1, Figure 2). No signs of direct nerve damage caused by the passage of either trochar or sling was found in any of the 6 pelves. The distance of the AdVance™ to the DNP did not show a significant difference between left and right. In 2 pelves (bodies 3 and 4, see Table 1), the tape was situated significantly further away from the DNP than in the other 4 pelves. The distance of the sling to the obturator neurovascular bundle was 30 mm or more in all 6 pelves.

Table 1 Distance of AdVance™ male sling to dorsal nerve of the penis

Distance to tape (mm)	Body 1	Body 2	Body 3	Body 4	Body 5	Body 6
Dorsal nerve of penis	L R	L R	L R	L R	L R	L R
AdVance™ male sling	0 2	4 5	10 7	10 9	0 2	0 0
Mean	4.1 mm.					

Discussion

This study aimed to visualize the anatomical relation between the DNP and the AdVance™ male sling.

Post-RP SUI because of sphincter incompetence is a well-known complication of the surgical treatment of prostate cancer. One of the recommended invasive treatment options for this type of SUI is the male sling procedure (4). During these past years, there has been an enormous rise in male sling surgery because of its minimally invasiveness and promising success rate (9).

The male sexual function is a complex combination of external and internal stimuli in which the sensory nerves of the penis play a vital role (6).The main sensory nerve of the penis, the DNP, is the final branch of the PN and runs medially to the inferior border of the IPR through the perineum (Figure 1). Damage to the DNP can cause both erectile

and orgasmic dysfunction and is therefore considered highly invalidating in sexually active men (7).

Damage to the DNP caused by the AdVance™ male sling procedure has not been noted or described in current literature. This anatomical study was performed following an AdVance™ procedure in our clinic that resulted in a unilateral neurotmesis of the DNP. Results showed a mean distance of the AdVance™ sling to the DNP of 4.1 mm (Table 1). Although the sling was found directly situated next to the DNP in 4out of12 (33%) hemipelves, none of the DNP showed any sign of direct damage by the trochar or sling (Table 1, Figure 2).

A literature search on anatomical studies describing the course of male slings produced one recent article by Pereira-Correia et al. that analysed the course of the Argus T™ (Promedon SA, Cordoba, Argentina) needles and sling in relation to the pelvic neuroanatomy. Although the authors extensively elaborate on the anatomical relation of the sling and the obturator neurovascular bundle, the proximity of the tape to the PN and DNP was not discussed (10).

Mid-urethral sling surgery in women is currently considered the preferred invasive treatment for curing SUI (4). The second generation midurethral slings (the Tension-free Vaginal Tape-Obturator and the Trans Obturator Tape) are placed through the foramen obturatorium using techniques similar to the one used in the AdVance™ male sling procedure (11–13). The dorsal nerve of the clitoris (DNC) in women is the anatomical equivalent of the DNP in men. A literature search using MeSH terms [pudendal neuralgia] and [suburethral sling] produced several articles on pudendal neuralgia following a trans-obturator sling procedure (14–16). However, none of these studies described incidents in which neurotmesis of the DNC occurred. Anatomical studies on the risk of injury to the DNC after mid-urethral sling placement through the foramen obturatorium in women showed that, hypothetically, the trochar and sling could come into contact with the DNC. Although these studies did not describe direct damage to the DNC; they clearly described the proximity of the trochars and sling to the DNC (17,18).

As the complication in our clinic could not be explained by precedents (male or female) in the current literature, and only partly by the anatomical study performed at this center, other explanations should be considered.

Firstly, there is the possibility that the complication of neurotmesis of the DNP was indeed encountered in other clinics as well, but has not been reported by either patients or physicians. Being a rare complication in a predominantly elder (and sexually inactive) population, this could at least partly explain the absence of any current literature on the subject.

Secondly, there is a chance that in our patient, the DNP had an aberrant course through the pelvis. Assuming this, the damage to the DNP could then have been suffered either during the surgical mobilization of the bulbar urethra or the placement of the

AdVance™. A recent study on the course of the PN and DNP does indeed show a high variability in different pelves (19). Unfortunately, as there is no way to ascertain the actual course of the DNP in our patient, this theory is purely hypothetical.

Thirdly, the DNP could have been damaged not during, but directly following the actual placement of the sling. After introduction, the AdVance™ is tensioned in order to reposition the urethral sphincter complex in the pelvis (8). During this process, the sling is in the close proximity or sometimes even directly adjacent to the DNP, as was described in the anatomical part of this study. After the sling has been tensioned, the plastic cover is removed from the mesh arms, uncovering the serrated edges that help secure the sling in the neighboring tissue (Figure 2). In theory, these serrated edges situated directly next to the DNP could potentially be responsible for nerve damage. Finally, the sling itself could have been placed incorrectly by the urologist, resulting in an abnormal route of either trochar or tape, and thus causing damage to the DNP. Although the specialist in our clinic was trained and educated in the placement of the AdVance™ by AMS, human error should always be taken into consideration when surgery is performed.

There are certain limitations to this study that have to be taken into consideration as well. The first limitation is that there were only 6 bodies used in this study, which makes it difficult to reproduce rare complications and draw conclusions concerning these complications. Moreover, the small number of bodies used limits the authors to present a logical explanation for the fact that in 2 pelves, the tape was situated significantly further away from the DNP than in the other 4 pelves (Table 1). In order to prove if diverging trajectories of the AdVance™ male sling are indeed encountered in the clinic as well, an in vivo study should be conducted on a larger scale.

The second limitation is the fact that the bodies used had no history of RP, whereas patients opting for the AdVance™ sling procedure usually do have a RP in their medical history. This difference could hypothetically result in an altered course of the AdVance™ sling in the dissected pelves and potentially bias results. On the other hand, a standard RP does not change the position of the DNP, as it lies in a different part of the pelvis. Second, the AdVance™ procedure uses the "outside–in" method, which ensures the initial course of trochar and sling is independent of the prostate. When introducing the trochar through the adductor muscles of the thigh, it first passes the obturator foramen (and the IPR) before it reaches the urethral bulb. The use of the outside-in method strengthens our opinion that these findings are independent of the fact whether or not a RP was performed.

Conclusions

The proximity of the AdVance™ to the DNP could potentially pose a risk that should be taken into consideration by physicians and patients when opting for surgery. Moreover, when introducing a new mid-urethral sling, an anatomical study should always include a description of the distal part of the neuro-anatomy in relation to the anatomical position of the sling.

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Summary (abstracts)

9

Chapter 1 provides an insight into the pathophysiology and history of surgical treatment of urinary incontinence in both male and female patients. Next (the rise of) sling surgery in urological and uro-gynecological practice is described and an overview is given of the methods of introduction of a new sling device on the commercial market. In the following section the relation between sling surgery, neurovascular damage and sexual functioning is discussed and the shortcomings of current literature are pointed out.

Finally the question is raised whether slings, old and new, for either male and female, can live up to the expectations of both patients and physicians by being both safe and effective in curing urinary incontinence. Secondly, we speculate whether sling surgery is anatomically safe with regard to those nervous systems which are essential for the sexual function or may actually be responsible for iatrogenic neurological damage during placement.

Chapter 2.1; The Introduction of mid-urethral slings: an evaluation of literature

Introduction and hypothesis

The objective of this study was to evaluate the degree and reliability of evidence used by manufacturers before the introduction of mid-urethral slings (MUS) onto the commercial market. Furthermore, minimum standards for marketed slings are recommended by evaluating recent suggestions for the introduction of gynecological meshes.

Methods

A systematic literature search was conducted using PubMed and commercial internet search engines in order to identify slings introduced by the industry over the last decade. Moreover, manufacturers were contacted by email, mail, and phone to provide data from before the introduction of the slings onto the commercial market. Once contact had been initiated, a 6-month deadline was set for data collection.

Results

Forty-one slings introduced between 1996 and 2012 were identified. Ten slings were described in a total of 20 studies with sample sizes varying from 10 to 368. The 41 MUS were produced by a total of 19 different companies. Seven companies never responded to recurrent emails, phone calls or other means of attempted contact. Thirty-one slings (76 %) remained without any comparative pre-launch data.

Conclusions

Mid-urethral slings were often introduced without any scientifically proven basis or pre-launch research. The US Food and Drug Administration and the European authorities should undertake immediate action by imposing strict rules before the launch of new MUS comparable with those recently suggested for meshes used in vaginal prolapse surgery.

Chapter 2.2; Erratum to: The Introduction of mid-urethral slings: an evaluation of literature presents relevant new information that became available on two slings after the publication of chapter 2.1.

Chapter 3; The MiniArc sling for female stress urinary incontinence: clinical results after 1-year follow-up

Introduction and hypothesis

The objective of this study was the assessment of the efficacy of the MiniArc for curing stress urinary incontinence.

Methods

Seventy-seven patients, operated on from March 2008 to November 2009, were evaluated in this study. One year postoperative data are presented. All patients suffered from predominant stress urinary incontinence. After 1 year, response was 74%. Evaluation was performed using a questionnaire consisting of the EuroQol-5 Dimensions, the Patient Global Impression of Improvement, the Incontinence Impact Questionnaire, the Urinary Distress Inventory, the Prolapse/Urinary Incontinence Sexual Questionnaire, short form, and the Defecation Distress Inventory.

Results

One year after surgery, 68% of the patients stated an improvement in their incontinence status, while only 44% stated to be completely dry.

Conclusion

The 1-year follow-up suggests that the MiniArc is less effective in the treatment of stress urinary incontinence than the TVT.

Chapter 4; Results of sling surgery in a non-selected population

Objective

To evaluate sling surgery in terms of effectiveness and quality of life, and describe the effects of confounding variables on outcomes.

Methods

A retrospective cohort study using multiple validated questionnaires was conducted in a specialized pelvic floor center in the Netherlands. Women were enrolled after undergoing sling surgery between January 1, 2010, and January 31, 2012. In addition to the preoperative questionnaire, participants completed a questionnaire a minimum of 6 weeks after surgery to assess outcomes.

Results

Of 255 eligible participants, 228 (89.4%) returned the postoperative questionnaire after a mean follow-up of 14.9 months (range 2–32). At the time of follow-up, 158 (69.3%) patients considered themselves cured and an improvement was observed in 155 (68.9%) patients. Seventy (31.1%) patients rated their postoperative situation as little

improved, unchanged or deteriorated. Compared to patients who had no history of previous related surgery, patients with prior sling surgery benefited significantly less from surgery, whereas those with concomitant vaginal surgery showed similar scores in all outcome parameters. A high body mass index was found to have a negative effect on the results of surgery.

Conclusion

Mid-urethral sling surgery is both efficient and effective in curing stress urinary incontinence. However, patient characteristics and confounding variables can influence the outcome of surgery and should therefore always be discussed with the patient.

Chapter 5; Results of collagen sling placement following the partial removal of a synthetic mid-urethral sling

Objective

To assess results of placement of the Pelvilace collagen sling following partial removal of a primary synthetic sling because of late complications.

Methods

A retrospective study was undertaken of patients with late complications after mid-urethral sling surgery who underwent placement of a Pelvilace sling at a center in the Netherlands between January 2006 and January 2011. A postoperative questionnaire was used to evaluate the continence status and continence-related quality of life. Patients scoring 0 in the Urogenital Distress Inventory stress symptoms section were considered cured. The subjective improvement or deterioration in symptoms was scored using the Patient Global Impression of Improvement (PGI-I).

Results

The questionnaire was completed and returned by 32 (84%) of 38 patients with a mean follow-up of 54.3 months. Nine (28%) patients were deemed cured. Among 29 patients who had not undergone a third surgery, the PGI-I showed a postoperative improvement in 14 (48%). The other 15 patients rated their postoperative situation as little improved, unchanged or deteriorated. Further sub-analysis showed clear differences in postoperative results between the different types of late complications (erosion and/or displacement).

Conclusion

The concomitant placement of a collagen sling following partial removal of a primary polypropylene sling shows reasonable results for specific complications.

Chapter 6; Sling surgery for the treatment of urinary incontinence after transurethral resection of the prostate: evaluation of literature and new data on the Virtue® male sling

Objective

To provide a review of literature regarding the role of male slings in the treatment of stress urinary incontinence (SUI) following a transurethral resection of the prostate (TURP) and to evaluate the effects of the Virtue® male sling in patients suffering from post-TURP SUI.

Materials and methods

A systematic review of literature was performed to identify all papers on the use of male slings in patients suffering from Post-TURP SUI. Secondly, a prospective cohort study was conducted on 8 patients who received the Virtue® as surgical treatment of post-TURP SUI. Questionnaires were collected preoperatively and 1, 3, 6 and 12 months postoperatively. Success and improvement were defined as pad usage (0 pads: success, pad reduction of ≥50%: improvement). The primary endpoint was the continence rate 1 year postoperatively. Data was analysed using the paired two-tailed *t*-test.

Results

Sling surgery appears to be significantly less successful in the treatment of SUI post-TURP when compared to other types of prostate surgery. The clinical trial on the Virtue® sling observed continence in 4 of 8 patients, with another 2 patients with improved continence after 1 year follow-up. No difference in success was observed between patients with mild and patients with severe SUI.

Conclusions

Little is currently known about the effects of sling surgery in patients with mild to severe SUI following a TURP. Although the Virtue® male sling seems to be an efficient and safe device in the treatment of this complication, longer follow-up and larger cohorts will be needed to further confirm these results.

Chapter 7; The somatic and autonomic innervation of the clitoris; preliminary evidence of sexual dysfunction after minimally invasive slings

Introduction

Vaginal sling procedures may have a negative effect on sexual function due to damage to vascular and/or neural genital structures. Even though autonomic innervation of the clitoris plays an important role in female sexual function, most studies on the neuroanatomy of the clitoris focus on the sensory function of the dorsal nerve of the clitoris (DNC). As of present, the autonomic and somatic pathways in relationship to sling surgery have not been described in detail.

Aim

The aim of this study is to reinvestigate and describe the neuroanatomy of the clitoris, both somatic and autonomic, in relation to vaginal sling procedures for stress urinary incontinence.

Methods

Serially sectioned and histochemically stained pelves from 11 female fetuses (10–27 weeks of gestation) were studied, and three-dimensional reconstructions of the neuroanatomy of the clitoris were prepared. Fourteen adult female hemipelves were dissected, after a tension-free vaginal tape (TVT) (7) or tension-free vaginal tape-obturator (TVT-O) (7) procedure had been performed.

Main Outcome Measures

Three-dimensional (3-D) reconstruction and measured distance between the clitoral nerve systems and TVT/TVT-O.

Results

The DNC originates from the pudendal nerve in the Alcock's canal and ascends to the clitoral bodies. In the dissected adult pelves, the distance of the TVT-O to the DNC had a mean of 9 mm. The cavernous nerves originate from the vaginal nervous plexus and travel at the 5 and 7 o'clock positions alongside the urethra. There, the autonomic nerves were found to be pierced by the TVT needle. At the hilum of the clitoris the branches of the cavernous nerves medially pass/cross the DNC and travel further alongside it. Just before hooking over the glans of the clitoris, they merge with the DNC.

Conclusion

The DNC is located inferiorly to the pubic ramus and was not disturbed during the placement of the TVT-O. However, the autonomic innervation of the vaginal wall was disrupted by the TVT procedure, which could lead to an altered lubrication-swelling response.

Chapter 8; Risk of damage to the somatic innervation of the penis during the AdVance™ male sling procedure; an anatomical study

Introduction

One of the methods to treat post radical prostatectomy stress urinary incontinence is the AdVance™ (American Medical Systems®, Minnetonka, MN, USA) male sling procedure. During this procedure, the somatic innervation of the penis may be at risk for injury. Six AdVance™ procedures were performed in 6 donated bodies at the Anatomy and Embryology Department of the Leiden University Medical Center. The pelves were dissected and the shortest distance between the sling and the dorsal nerve of the penis (DNP) was documented.

Aim

The aim of this study was to describe the anatomical relation between the AdVance™ male sling and penile nerves based on the dissection of 6 adult male pelves.

Methods

The AdVance™ male sling procedure was conducted in 6 donated male bodies. After placement, the pelves were dissected and the shortest distance between sling and the DNP was documented.

Main Outcome Measure

The main outcome measure was the distance between the AdVance™ male sling and the DNP

Results

The mean distance of the sling to the DNP was 4.1 mm and was found situated directly next to the nerve (distance 0 mm) in 4 out of 12 (33%) hemipelves. The distance of the sling to the obturator neurovascular bundle was 30 mm or more in all 6 bodies.

Conclusions

Damage to the DNP caused by the AdVance™ male sling procedure appears to be an extremely rare complication, which has not been described in current literature. The proximity of the AdVance™ to the DNP could, however, pose a risk that should be taken into consideration by physicians and patients when opting for surgery.

Discussion and conclusion

10

Introduction

This thesis starts with the question whether slings, old and new, for both male and female patients, can live up to the expectations of both patients and physicians by being both safe and effective in curing stress urinary incontinence (SUI). Secondly, the question is raised whether sling surgery is anatomically safe with regard to those nervous systems that are essential for the sexual function or may actually be responsible for iatrogenic neurological damage during placement.
We addressed these questions by critically evaluating the methods of introduction, the efficacy and the (anatomical) safety of various slings used for curing SUI.

Main findings

The first part of the research question was addressed by evaluating the methods of introduction and efficacy of both old and new slings (chapter 2-4). In **chapter 2** the methods of introduction of new mid-urethral slings (MUS) were assessed and it was revealed that there is a lack of pre-launch data in more than 70% of the marketed slings. In **chapter 3** we presented the clinical results of a 'new generation' sling, the MiniArc™, in a population of 77 women after 1 year. These results show that only 44% of the patients was (subjectively) cured after 1 year, suggesting that the MiniArc™ is less effective in the treatment of SUI than the TVT™.
Chapter 4 describes the results of sling surgery in a non-selected population of 255 women after a mean follow-up of 15 months. The conclusion of this study was that, although sling surgery is both effective and efficient in curing SUI, patient characteristics and confounding variables can seriously influence the outcome of surgery and should therefore always be discussed with the patient. Moreover, the results of chapter 4 confirmed the beneficial effects of simultaneous pelvic organ prolapse (POP) surgery and MUS placement as this provided significant improvements in both urinary symptoms and QoL, without any negative effects in terms of SUI related symptoms.
The thesis continues in **chapter 5** with a clinical article that discusses the beneficial effects of concomitant collagen sling placement following partial removal of a primary synthetic MUS due to late complications (erosion and/or displacement). The outcome of this study was that, although this procedure shows some promising results for specific complications in terms of continence, more research on the individual approach of late complications will be needed in the future. Despite the fact that this chapter did not aid in answering the research question as such, it does shed (some) light on the complexity and diversity of (late) complications that can arise following sling surgery.

A review of literature on the results of sling surgery in male patients suffering from urinary incontinence following a transurethral resection of the prostate (TURP) is provided in **chapter 6**, together with an evaluation of a new sling (Virtue®) in this specific group. The review shows that literature on this subject is scarce and suggests that sling surgery in this group is significantly less successful in comparison to other patient groups. The clinical trial on the Virtue® sling observed continence in 4/8 (50%) patients, with another 2 (25%) patients stating an improvement in their SUI at the 12-month postoperative follow-up. This paper concluded that the new Virtue® sling shows promising results in being an efficient and safe device for the treatment of SUI following a TURP, but larger cohorts will be needed to confirm these results.

The final 2 chapters answer the second part of the research question by describing the potential perioperative damage caused by sling surgery to the pelvic (neuro) anatomy in male and female patients. In **chapter 7** the autonomic and somatic pelvic pathways and their relationship to the TVT™ or TVT-O™ were assessed by the dissection of 14 female hemi-pelves. Moreover a three-dimensional reconstruction of the neuroanatomy of the clitoris was created by studying serially sectioned and histochemically stained pelves from 11 female fetuses. The results showed that the dorsal nerve of the clitoris (DNC) is located inferiorly to the pubic ramus and was not disturbed during the placement of the TVT-O™. However, the autonomic innervation of the vaginal wall was disrupted by the TVT™ procedure, which could lead to an altered lubrication-swelling response.

Chapter 8 starts with the description of a patient in which the AdVance™ male sling procedure resulted in the complete interruption, or neurotmesis, of the right dorsal nerve of the penis (DNP). Due to this complication, a study was conducted to further describe the anatomical relation between the AdVance™ male sling and the DNP based on the dissection of 6 adult male pelves. Results of this study showed a mean distance between the sling and DNP of 4.1 mm, whilst it was situated directly next to the DNP in 4 out of 12 (33%) hemi-pelves. The distance of the sling to the obturator neurovascular bundle was 30 mm or more in all 6 bodies. In conclusion, although damage to the DNP caused by the AdVance™ male sling procedure appears to be an extremely rare complication, the proximity of the AdVance™ to the DNP could possibly pose a risk that should be taken into consideration by physicians and patients when opting for surgery.

Implications and recommendations

The introduction of new slings

New slings are often introduced without any structured scientific pre-launch evidence on their effectiveness and safety (1;2). In April 2014, the U.S. Food and Drug Administration (FDA) issued two proposed orders for the re-classification of surgical meshes used for transvaginal pelvic organ prolapse (POP) repair. The first order would re-classify these medical devices from class II, which generally includes moderate-risk devices, to class III, which generally includes high-risk devices. The second order would require companies to provide clinical data in a premarket approval (PMA) application to support the safety and effectiveness of the device. On the fifth of January 2016 the FDA issued their final orders for the reclassification of these products and the requirement of a PMA. However, the FDA also clearly stated that these orders do not include surgical meshes indicated for the surgical treatment of SUI, meaning that these slings can still be introduced without any supporting premarket evidence (*).
We believe that in order to achieve the best and safest possible products for patients new standards should also be introduced for the marketing of slings as soon as possible. These standards should include the four obligatory points shown below, followed by a compulsory registration of the first 1,000 consecutive patients (1).

1. *Comprehensive and exact data on the physical properties of the product*
2. *Data on the biological properties of the product following implantation from high-quality animal studies*
3. *Anatomical studies on cadavers*
4. *A well-constructed and documented cohort study*

The results of the MiniArc™ in chapter 3 further illustrate the fact that a new product and technique is not necessarily equal to, or better than, a gold standard such as the TVT™ (3). The disappointing results, combined with the fact that no premarket studies had been performed on this particular sling, strengthen our belief that new standards for the introduction of new slings are indeed very much needed. In the future these new standards should be able to prevent inferior or even dangerous products from reaching the market and will ultimately result in better patient care.

* (https://www.federalregister.gov/articles/2016/01/05/2015-33163/effective-date-of-requirement-for-premarket-approval-for-surgical-mesh-for-transvaginal-pelvic-organ), http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm262301.htm

Individuality in informed consent and approach of late complications

As no two patients are equal, it can be derived that not every patient will benefit equally from the same surgical procedure. This also applies to MUS surgery and according to the EAU guideline these confounding variables could play a large role in determining the outcome of surgery (4). Current research on MUS surgery frequently tends to exclude patients with confounding variables and only present results of the 'perfect' patient group (BMI<35, no surgical history, no concomitant surgery etc.) (5-8).

In chapter 4 we showed that when a study is performed on a 'raw' and non-selected population overall results may indeed be disappointing at first sight. If however a population is large enough to perform subgroup analysis, one can then accurately describe and compare the results of the individual patient groups. Future studies on MUS surgery should therefore aim to minimize their selection bias, rather than just present the results of the 'perfect patient'. This information can and should then be used to provide more individualised informed consent and prevent overestimating the outcome of surgery (9).

When a surgical procedure is as regularly performed as sling surgery, it will inevitably lead to higher numbers of (postoperative) complications. Two of the most common late postoperative complications of sling surgery in women are erosion of the mesh material and displacement of the tape towards the bladder neck. Still, where local treatment such as cleaving the sling may be possible in some, the complete or partial removal of the mesh material is unavoidable in others. If a primary sling is (partly) removed after erosion or displacement in an incontinent patient, the concomitant placement of a second sling should theoretically enhance postoperative continence levels. In chapter 5 we observed that this was in fact not the case, as continence was achieved in less than one-third of our study population (10). The analysis of the, somewhat disappointing, results together with a review of literature showed that studies on this subject are rare and that, although some patients are seemingly suffering from a similar problem, there is no such thing as a general approach when dealing with rare complications (11-14). In conclusion we can say that when dealing with such a complex population, every specific case has to be approached as being a unique problem on itself. Moreover it becomes clear that mid-urethral slings can be responsible for a significant loss in quality of life due to late complications and more research on the individual approach of specific complications will be needed in the future to provide optimal patient care.

Sling surgery for male patients with SUI

When discussing postoperative (iatrogenic) SUI in male patients, the causes can be divided into two main groups; the first following a radical prostatectomy (RP), the second following a TURP. Complication rates following a TURP are generally low but are frequently encountered following the large number of surgical procedures. SUI

after a TURP occurs in 1.8% to 5.0% of patients (15-18). While sling surgery following a RP is becoming increasingly popular and shows respectable success rates between 40 and 91%, little is actually known about the efficacy in patients following a TURP (19;20). A literature search on this matter revealed that there are only a few studies describing a handful of TURP patients, but success rates are generally lower than in patients following a RP (21-25). The results of the small case series in chapter 6 showed that, in contrast to other slings in current literature, the Virtue® male sling appears to be as effective in post-TURP patients as in patients with a RP in their medical history. To review these preliminary findings from a scientific perspective, knowledge on the actual pathophysiology of iatrogenic SUI is paramount. Whereas SUI following a RP may be caused by either sphincter dysfunction or bladder dysfunction, SUI following a TURP is usually caused by damage to the proximal part of the (rhabdo) sphincter distal to the seminal colliculus or verumontanum (26). The dual design of the Virtue® male sling that combines both perineal urethral compression and proximal urethral relocation, support our hypothesis that this sling is better suited for post-TURP SUI than other conventional male slings that work through either compression or relocation of the urethra (27-31).

When looking at the results of sling surgery for male SUI, one has to take into consideration that the surgical gold standard, in this predominantly older patient group, still is the complication prone AUS (artificial urethral sphincter). So, understandably, the relatively minimally invasive male slings have gained popularity in the treatment of SUI over the last two decades. Nevertheless it remains the question whether sling surgery is indeed the treatment of the future for the specific group described in this thesis and more research on the subject will be needed.

Sling surgery and sexual function

Vaginal sling procedures may have a negative effect on sexual function through neurovascular damage to the genital structures. To discern between the possible negative effects due to neurovascular damage in combination with the positive side-effects on sexual functioning of the surgical procedure itself (regaining continence), is virtually impossible. By describing the anatomical relationship between the somatic and autonomic pathways of the clitoris and the TVT™/TVT-O™ in chapter 7 of this thesis, more light was shed on this intricate question. The proximity of the autonomic nerves of the clitoris and the TVT™, means that this procedure will almost certainly cause neurological damage that may result in disturbances in the swelling and lubrication response during arousal. These findings are retrospectively confirmed by a study by Caruso et al. in 2007, which showed a significant decrease in the clitoral blood flow after a TVT™ procedure (32). Furthermore the proximity of the DNC and the TVT-O™ shows that, although rare, neurological damage could occur during surgery (33).

In the future these possible negative side-effects on sexual function should be a standard part of the informed consent provided when opting for surgery and could eventually lead to different groups of patients selecting different slings as a result of this information.

In chapter 8 this thesis continues with a paper that further clarifies the (neuro-) anatomical relationship between the AdVance™ male sling and the DNP. Based on basic anatomical knowledge, it can be estimated that the anatomical route of a male transobturator sling, such as the AdVance™, is close to certain important urogenital nerves such as the DNP. When consulting the literature on this subject it is safe to say that the complication encountered in our clinic (neurotmesis of the DNP) is indeed very rare, but any substantial anatomical research since the introduction of this sling, other than the study in this thesis, is lacking.

In an editorial comment on this chapter, the author questions the methodology and validity of the clinical implications based on the conclusions of this paper. In our conclusion we state that the proximity of the AdVance™ to the DNP could potentially pose a risk that should be taken into consideration by physicians and patients when opting for surgery. Nonetheless, by claiming that there is no proven clinical risk and numbers in our study are lacking, the need to inform patients of this potential risk is dismissed. In contrast, the study itself is commended (34). In another response to our paper by the inventor of the AdVance™ in an expert's summary, the author first points out certain limitations in the methodology of this study and then emphasizes the fact that in his clinical experience, the complication of neurotmesis of the DNP has never been encountered (35).

From the reactions on both chapter 7 and 8 there are several lessons to be learned. Firstly it is nearly impossible to extrapolate the findings of a relatively small in mortuo study directly into a clinical setting without substantial 'in vivo' functional evidence to back up the findings. Secondly, when conducting basic in mortuo anatomical research on this scale, the lack in numbers and the (obvious) difference between cadaveric and live tissue will always remain a valid argument to challenge the substance of such a study.

This leaves us with the next dilemma; is it enough for a small(er) study to act as a thought provoking contribution to our knowledge, or should it have clinical consequences as well? As of present, a (central) registry to track the outcomes and adverse events of (new) slings does not exist and basic anatomical research on this subject remains rare. The lack of such a registry will always make it difficult to put the findings of smaller observational studies into perspective and make clinical recommendations. In the end, whether a surgeon chooses to merely acknowledge the information, or actually uses it to inform his or her patients, remains up to them. Nevertheless, taking the tens of thousands of slings being implanted around the world each year into consideration,

it is obvious that more research should be conducted to investigate these potential surgical complications.

Future perspectives and conclusion

Will sling surgery remain the treatment of choice in the endless battle against SUI? Can newer techniques make sling surgery even less invasive (and safer) without compromising the success rate? Will new standards to monitor the introduction and marketing of new slings be introduced in the near future? Or will sling surgery be replaced altogether by a new treatment that focuses on urethral function rather than urethral support?
These are all questions that remain unanswered up to present. It is clear however that these last decades (synthetic) slings have made a huge, and largely positive, impact on the treatment of urinary incontinence. Nevertheless, the medical community should always strive to provide the best and safest care possible for its patients, meaning one has to assure him- or herself on the safety and efficacy of a new medical device before using it in practice. In this thesis we conclude that many slings were, or still are, freely available on the market without any proper pre-market research. By conducting structured studies adhering to predetermined protocols, that include both in vivo as well as ex vivo elements, prior to the introduction of a new sling, combined with the introduction of a central registry to track the outcomes and adverse events of new slings, a safer patient environment can and should be created in the future.

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Nederlandse samenvatting
Curriculum Vitae
List of publications
List of abbreviations
Woord van dank

11

Nederlandse samenvatting

Nederlandse samenvatting

Incontinentie voor urine is een veel voorkomende ziekte die zijn weerslag heeft op miljoenen mensen (zowel vrouwen als mannen) wereldwijd. Ondanks dat urineverlies geen dodelijke aandoening is, wordt het geassocieerd met negatieve effecten op meerdere aspecten van het leven en wordt het door patiënten vaak als een grote last gezien. Stress urine-incontinentie (SUI) is de meest voorkomende vorm van incontinentie en wordt gedefinieerd als urineverlies bij een verhoging van de intra-abdominale druk, zoals bij hoesten, niezen of lachen. Recente studies in de Westerse wereld schatten dat zo'n 60% van de vrouwen tussen de 14 en 64 jaar te maken heeft met SUI, met zelfs nog hogere percentages voor de oudere generaties. Bij mannen wordt de prevalentie van urine-incontinentie geschat op 11% in de groep van 60-64 jaar en zelfs op 33% boven de 65 jaar. De meest voorkomende vorm van urine-incontinentie bij mannen is de zogenaamde 'aandrang' incontinentie (urge-incontinentie, 40-80% van de gevallen), terwijl stressincontinentie in deze groep vaak het gevolg is van prostaat gerelateerde operaties.

De afgelopen honderd jaar zijn er tientallen verschillende operaties en technieken voor de behandeling van stressincontinentie bij vrouwen ontwikkeld, maar geen werd er zo succesvol als de zogenaamde 'mid-urethrale sling' (MUS). De eerste echt succesvolle mid-urethrale sling, de TVT, werd in 1996 door de Zweedse gynaecoloog Ulmsten geïntroduceerd. Dankzij het minimaal invasieve karakter, gecombineerd met een hoge effectiviteit en veiligheid, wordt deze ingreep sindsdien gezien als de goudstandaard voor de chirurgische behandeling van SUI. In een poging een graantje mee te pikken van het succesverhaal van de TVT zijn er de afgelopen jaren tientallen vergelijkbare nieuwe slings geïntroduceerd met wisselende getallen voor zowel effectiviteit als veiligheid. Ook bij mannen zijn de slings tegen SUI de afgelopen 15 jaar aan een opmars begonnen, hoewel solide bewijs voor de werking en veiligheid van deze helaas nog vaak afwezig blijkt te zijn.

In de introductie van dit proefschrift (**hoofdstuk1**) wordt aan de hand van enkele paragrafen het onderwerp van dit proefschrift geïntroduceerd; namelijk de chirurgische behandeling van SUI door middel van slings. De vraag die in dit proefschrift centraal staat is of deze slings, oud of nieuw, voor vrouwen of voor mannen, hun belofte naar arts en patiënt waar kunnen maken door SUI op een veilige en effectieve manier te genezen. Om deze vraag te kunnen beantwoorden werden de verkrijgbare slings, die gebruikt worden in de hedendaagse urogynaecologische en urologische praktijk, geëvalueerd vanuit een klinisch en anatomisch oogpunt. Tevens werd er in meerdere hoofdstukken aanvullend literatuuronderzoek betreffende sling chirurgie verricht.

In **hoofdstuk 2** van dit proefschrift werd er gekeken met welk bewijs nieuwe slings door producenten op de medische markt werden geïntroduceerd. Om dit in kaart te

brengen werden er eerst zoveel mogelijk vrij verkrijgbare slings geïdentificeerd. Vervolgens werden de producenten benaderd om data te verstrekken omtrent de veiligheid en effectiviteit van de desbetreffende sling, voorafgaand aan de introductie op de markt. Na het leggen van contact kreeg het bedrijf 6 maanden de tijd om de gevraagde informatie aan te leveren.
In deze studie werden er 41 slings (geïntroduceerd tussen 1996 en 2012) geïdentificeerd, waarvan er 10 werden beschreven in een totaal van 20 studies. De 41 slings werden gemaakt door 19 verschillende bedrijven, waarvan er 7 niet hebben gereageerd op herhaaldelijke verzoeken contact met ons op te nemen. Eenendertig van de 41 slings (76%) bleken uiteindelijk zonder enige vorm van vergelijkend onderzoek te zijn geïntroduceerd.
Concluderend kunnen we stellen dat nieuwe slings vaak worden geïntroduceerd zonder enige vorm van vergelijkend onderzoek en dat Amerikaanse en Europese autoriteiten zo snel mogelijk actie moeten ondernemen om dit te stoppen. Naar aanleiding van deze conclusie wordt de discussie van dit hoofdstuk afgesloten met een reeks nieuwe aanbevelingen voor de introductie van nieuwe slings, mede gebaseerd op recente suggesties voor de introductie van gynaecologische meshes (polypropyleen matten) welke worden gebruikt bij verzakkingsoperaties.
Als addendum van hoofdstuk 2, wordt er in **hoofdstuk 2.2** nieuwe informatie verschaft over 2 slings, welke pas beschikbaar kwam na de publicatie van hoofdstuk 2.
De MiniArc™ is een zogenaamde 'minisling' welke is ontwikkeld om SUI minder invasief, maar net zo effectief en veilig te behandelen als met de originele TVT. **Hoofdstuk 3** beschrijft de resultaten van deze MiniArc™ in 77 patiënten na 1 jaar. Na 1 jaar follow-up bleek dat slechts 44% van de patiënten volledig continent was, met een verbetering van het urineverlies in 68%. De conclusie van deze studie is dan ook dat, ondanks beloftes van de producent, de MiniArc™ minder effectief is voor de operatieve behandeling van SUI dan de TVT.
Het proefschrift gaat vervolgens verder met **hoofdstuk 4**, waarin een retrospectieve cohort studie wordt beschreven welke werd verricht om de effectiviteit en veiligheid van mid-urethrale slings voor SUI in een 'ongezuiverde' (dat wil zeggen: niet voorgesorteerd op basis van bijvoorbeeld leeftijd of gewicht) populatie vrouwen te bekijken. Tevens werd in dit hoofdstuk gekeken naar de invloed van verschillende patiënt specifieke eigenschappen op de uitkomst van de ingreep. Patiënten die tussen 1 januari 2010 en 31 januari 2012 werden geopereerd in het bekkenbodemcentrum van het Albert Schweitzer ziekenhuis te Dordrecht werden geïncludeerd. Deze groep patiënten werd vervolgens verzocht om vragenlijsten in te vullen voorafgaand en minimaal 6 weken na de ingreep.
In totaal werden er 255 patiënten geïncludeerd, waarvan er 228 (89.4%) de postoperatieve vragenlijst terugstuurden met een gemiddelde follow-up van 14.9 maanden

(range 2-32 maanden). Op het moment van invullen van de postoperatieve vragenlijst beschouwde 158 (69.3%) patiënten zichzelf als genezen, terwijl 155 (68.9%) hun postoperatieve situatie met betrekking tot de SUI (sterk) verbeterd vond. Zeventig van de geïncludeerde vrouwen (31.1%) gaf aan dat de SUI postoperatief weinig verbeterd of zelfs verslechterd was.
Sub-analyses toonden vervolgens aan dat, in vergelijking met patiënten zonder verleden van incontinentie chirurgie, patiënten met een sling operatie in de voorgeschiedenis aanzienlijk minder baat hadden van een tweede operatie met een MUS. Patiënten die tegelijkertijd met de sling ook een vaginale ingreep (bijvoorbeeld correctie van een verzakking) ondergingen bleken het net zo goed te doen als de patiënten die enkel de sling kregen. Bovendien bleek een hoog BMI (body mass index) een negatief effect te hebben op de uitkomst van de ingreep.
Naar aanleiding van deze studie kunnen we concluderen dat sling chirurgie zowel efficiënt als effectief is in de operatieve behandeling van MUS. Tevens kunnen we stellen dat patiënteigenschappen en andere variabelen, zoals operaties in het verleden, de uitkomst van de ingreep kunnen beïnvloeden en daarom te allen tijde van tevoren besproken dienen te worden met de patiënt in kwestie.
Tot op heden is er geen standaard ingreep voor de operatieve behandeling van late complicaties, zoals erosie of verplaatsing, na het krijgen van een MUS. In **hoofdstuk 5** worden de resultaten beschreven van een chirurgische procedure na het optreden van late complicaties, waarbij een oude sling deels verwijderd werd en er meteen een nieuwe collageen sling werd geplaatst .
In totaal ondergingen 38 patiënten tussen januari 2006 en december 2010 deze ingreep in een derdelijns ziekenhuis in Nederland. Postoperatief werd alle patiënten verzocht speciaal ontworpen vragenlijsten in te vullen om zo het effect van deze ingreep te kunnen evalueren. Deze studie toonde aan dat van de 32 patiënten (84%) die participeerden in het onderzoek, slechts 28% continent was na een periode van gemiddeld 54 maanden, met een verbetering van de klachten in 44% van de studiegroep (14/32). De overige 18 patiënten (56%) bleken weinig of geen baat bij deze ingreep te hebben op het vlak van incontinentie. Verdere sub-analyses lieten duidelijke verschillen zien tussen de postoperatieve resultaten in de verschillende groepen van complicaties (erosie en/of verplaatsing).
Concluderend kunnen we naar aanleiding van dit onderzoek stellen dat het plaatsen van een collageen sling na het verwijderen van een primaire synthetische sling redelijke resultaten in specifieke groepen oplevert.
De transurethrale resectie van de prostaat (TURP) in verband met benigne prostaathypertrofie (BPH) is een ingreep die veelvuldig wordt verricht in vrijwel iedere urologische praktijk. Één van de meest voorkomende complicaties na een TURP is SUI welke wordt veroorzaakt door peroperatieve beschadiging van de sluitspier. .

Hoofdstuk 6 beschrijft een literatuuronderzoek naar de effectiviteit van sling chirurgie voor SUI ten gevolge van een TURP. Verder worden er in een prospectieve studie 8 patiënten gevolgd welke een ingreep ondergingen met de Virtue® sling voor de behandeling van hun post-TURP SUI. De uitkomst van deze studie was dat sling chirurgie na een TURP significant minder goede resultaten gaf dan sling chirurgie bij patiënten met SUI na andere vormen van prostaatchirurgie (zoals een radicale prostatectomie). Het klinische deel toonde dat 1 jaar na operatie met de Virtue® 4 van de 8 patiënten (50%) volledig continent waren, terwijl nog eens 2 patiënten (25%) verbetering van de incontinentieklachten ondervonden. Bovendien werd er gezien dat de ernst van incontinentie (mild of ernstig) geen invloed had op het al dan niet succesvol functioneren van de sling.
Naar aanleiding van dit onderzoek kunnen we stellen dat er er weinig bekend is over de effecten van sling operaties in mannen met SUI na een TURP. De resultaten van de Virtue® in deze beperkte trial zijn desalniettemin hoopvol voor de toekomst. Wel zullen er grotere cohorten met langere follow-up nodig zijn om deze resultaten te kunnen bevestigen.
Neuro-anatomische studies naar slings voor de operatieve behandeling van SUI zijn relatief zeldzaam en worden slechts zelden gevonden in de huidige literatuur. In **hoofdstuk 7** en **hoofdstuk 8** wordt er gekeken naar de mogelijke bijeffecten van sling chirurgie vanuit een neuro-anatomisch oogpunt. In deze hoofdstukken wordt door middel van twee studies de anatomische 'route' van een drietal slings in het vrouwelijke (2) en mannelijke bekken (1) onder de loep genomen om zo meer inzicht te krijgen in de mogelijke zenuwschade veroorzaakt door de ingreep. Deze zenuwschade kan namelijk van grote invloed zijn op het postoperatief seksueel functioneren van de patiënt en is daarom van groot belang voor het welzijn.
Hoofdstuk 7 beschrijft de mogelijke schade aan het autonome zenuwstelsel (de plexus hypogastricus inferior, belangrijk voor de zwelling en lubricatie bij opwinding) en het somastische zenuwstelsel (de dorsale zenuw van de clitoris, verantwoordelijk voor het gevoel) van de clitoris, veroorzaakt door de TVT (Tension-free Vaginal Tape) en TVT-O (Tension-free Vaginal Tape-Obturator).
Een driedimensionale reconstructie, gemaakt door coupes van foetale bekkens histochemisch in te kleuren, toont zowel de autonome als de somatische zenuwen van de clitoris in detail. Belangrijk hierbij is de bevinding dat de dorsale zenuwen van de clitoris langs de mediale zijde van de ramus inferior van het os pubis richting de clitoris lopen om uiteindelijk samen met de autonome zenuwen de clitoris in te duiken. In het tweede deel van deze studie werden er 14 gehalveerde volwassen bekkens van gedoneerde lichamen uitgeprepareerd, nadat hierbij in een eerder stadium een TVT (7) of TVT-O (7) was geplaatst. De preparaten toonden aan dat de dorsale zenuw van de clitoris mogelijk risico loopt op beschadiging bij het plaatsen van een TVT-O, terwijl de autonome innervatie van de clitoris juist kan worden verstoord door de TVT procedure.

In **hoofdstuk 8** werd er gekeken naar de relatie tussen de dorsale zenuw van de penis (deze verzorgt het gevoel van de penis en is zeer belangrijk bij zowel de erectie als het orgasme) en de AdVance™ male sling naar aanleiding van een complicatie in onze kliniek. Om deze relatie verder te onderzoeken werd de AdVance™ procedure uitgevoerd op 6 mannelijke, aan de wetenschap gedoneerde lichamen, waarvan vervolgens de bekkens werden uitgeprepareerd. De preparaten lieten zien dat de AdVance™ in 4 van de 12 (33.3%) hemi-bekkens direct tegen de dorsale zenuw aanlag, zonder deze direct te hebben beschadigd. Deze afstand van de sling tot de zenuw betekent echter wel dat er sprake is van een potentieel risico dat van tevoren door zowel arts als patiënt in overweging moet worden genomen.

Toekomstperspectieven en conclusie

Zal sling chirurgie ook in de toekomst de aangewezen methode blijven voor de operatieve behandeling van stressincontinentie? Zullen nieuwe technieken de sling chirurgie (nog) minder invasief en veiliger maken, zonder dat dit ten koste zal gaan van de effectiviteit van de ingreep? Zullen er in de nabije toekomst betere maatregelen worden getroffen om de introductie en marketing van nieuwe slings beter te monitoren? Of zal deze vorm van chirurgie uiteindelijk in zijn geheel verlaten worden voor een methode die zich meer toelegt op de functionaliteit van de urethra en niet zozeer de ondersteuning. Al deze vragen blijven tot op heden onbeantwoord. Wat echter wel overduidelijk is, is dat de introductie van de synthetische sling de afgelopen decennia een enorme en overwegend positieve invloed heeft gehad op de operatieve behandeling van stressincontinentie.

Dit gezegd hebbende kunnen we op basis van dit proefschrift concluderen dat er tot op heden vele slings vrij op de markt verkrijgbaar zijn zonder enige vorm van adequaat onderzoek voorafgaand aan de introductie. Het blijft echter de taak van de medische professional om te allen tijde zorg te dragen voor de beste en veiligste behandelmethodes voor zijn of haar patiënten. Dit laatste betekent dat een arts zich eerst zal moeten vergewissen van de veiligheid en effectiviteit van een nieuw medisch (hulp)middel, alvorens dit daadwerkelijk in de praktijk toe te passen.

In de toekomst zullen er studies, gestructureerd volgens vaste protocollen, met zowel in vivo als ex vivo onderdelen, voorafgaand aan de introductie van nieuwe slings uitgevoerd moeten worden. Daarnaast zal er een centrale registratie opgezet moeten worden om de uitkomsten en complicaties van nieuwe slings te monitoren. Alleen door deze voorwaarden zo spoedig mogelijk te implementeren kan de veiligheid van de behandeling van stressincontinentie met behulp van slings in de toekomst worden gegarandeerd.

Curriculum Vitae

Curriculum Vitae

Cornelis (Kees) Hogewoning was born on February 3rd 1987 in Rotterdam, the Netherlands. He grew up in Dordrecht with a younger brother and older sister and graduated in 2005 from the Johan de Witt Gymnasium. With the ambition of becoming a doctor he enrolled for the study of medicine but was eliminated by numerus fixus. After a year at the Faculty of Veterinary Medicine of the University of Ghent, he started his medical degree at Leiden University in 2006.
During his studies he worked as a tissue explanter for the BIS foundation, was an active member of the student society 'Minerva', and became a dedicated rugby player for LSRG and DIOK.
In the winter of 2010 he performed his first research project on the MiniArc sling at the department of Urology under the supervision of Dr. M.D. Bekker, after which he was offered a position as a PhD candidate by Dr. H.W. Elzevier. In the following year he officially started his PhD research at the departments of Urology and Anatomy-Embryology of the Leiden University Medical Center under the supervision of Dr. H.W. Elzevier, Prof. dr. R.C.M. Pelger and Prof. dr. M.C. de Ruiter. During this year multiple projects were initiated and various data on sling surgery and genital neuro-anatomy was gathered. He presented his work at several meetings, including the International Urogynecological Association (IUGA) and the European Society for Sexual Medicine (ESSM).
From 2012 to 2014 he continued his medical training and obtained his medical degree in May 2014. In November 2014 he started as a non-training urology resident at the Medisch Centrum Haaglanden in The Hague (Drs. C.P.A.M. Berger). In September 2015 he was admitted as a urology trainee and in January 2016 he started his general surgery residency at the HagaZiekenhuis, The Hague. His urological training will continue in 2018 at the Leiden University Medical Center and the Hagaziekenhuis.

List of publications

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Articles

Cornelis R.C. Hogewoning, Inge M. C. Ruhe, Milou D. Bekker, Rob. C. M. Pelger, Cornelis J. A. Hogewoning, Hein Putter, Marco C. DeRuiter, Henk W. Elzevier
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(De introductie van mid-urethrale slings, een evaluatie van de huidige literatuur
Tijdschrift voor Urologie, October 2014, Volume 4, Issue 7, pp 160-160)

List of abbreviations

List of abbreviations

AMS:	American Medical Systems
AUS:	Artificial urethral sphincter
BMI:	Body Mass Index (kg/m^2)
CE:	Conformité Européenne
CN:	Cavernous nerves of clitoris
DNC:	Dorsal Nerve of Clitoris
DNP:	Dorsal Nerve of Penis
EAU:	European Association of Urology
EQ-5D:	5-Dimensional EuroQol instrument
FDA:	US Food and Drug Administration
ICS:	International Continence Society
IHP:	Inferior Hypogastric Plexus
IIQ:	Incontinence Impact Questionnaire
IPR:	Inferior pubic ramus
IUGA:	International Urogynecological Association
KHQ:	King's Health Questionnaire
MeSH (terms):	Medical Subject Headings
MUCP:	Maximum urethral closing pressure
MUS:	Mid-urethral sling
NO:	Nitric oxide
PGI-I:	Patients Global Impression of Improvement
PIS-Q:	Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire
PMA:	Premarket approval
PN:	Pudendal nerve
POP:	Pelvic organ prolapse
PPD:	Pads per day
RP:	Radical prostatectomy
QoL:	Quality of life
SD:	Standard deviation or Sexual Dysfunction (depending on context)
SUI:	Stress urinary incontinence
TOT:	Trans Obturator Tape
TUR-P:	Transurethral resection of the prostrate
TVT:	Tension-free Vaginal Tape
TVT-O:	Tension-free Vaginal Tape-Obturator
TVT-S:	Tension-free Vaginal Tape-Secur
UDI:	Urogenital Distress Inventory
UI:	Urinary incontinence
VAS:	Visual analogue scale

Woord van dank

Woord van dank

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