The urethral closure function in continent and stress urinary incontinent women assessed by Urethral Pressure Reflectometry

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THE FOUR ORIGINAL PAPERS ARE

1. Saaby ML, Klarskov N, Lose G. Urethral pressure reflectometry before and after tension-free vaginal tape. Neurourol Urodyn. 2012;31(8):1231-5.
2. Klarskov N, Saaby ML, Lose G. A faster urethral pressure reflectometry technique for evaluating the squeezing function. Scand J Urol. 2013;47(6):529-33.
3. Saaby ML, Klarskov N, Lose G. Urethral pressure reflectometry during intra-abdominal pressure increase-an improved technique to characterize the urethral closure function in continent and stress urinary incontinent women. Neurourol Urodyn. 2013;32(8):1103-8.
4. Saaby ML, Klarskov N, Lose G. The impact of tension-free vaginal tape on the urethral closure function: mechanism of action. Accepted for publication 2013, Neurourol Urodyn.

INTRODUCTION

URINARY INCONTINENCE

Urinary incontinence (UI) is a major health issue among women with a prevalence of about 35 % (1). Most patients (70 – 75 %) have stress urinary incontinence (SUI) (leakage in connection with physical effort or exertion, or when sneezing or coughing) either pure or in combination with urgency or urgency urinary incontinence (leakage accompanied or immediately proceeded by a compelling desire to void). Treatment modalities comprise conservative aids (lifestyle changes, pelvic floor muscle training and pharmacological therapy) while especially those with significant quality of life problems may require surgical therapy.

The underlying cause of SUI is insufficiency of the urethral closure mechanism during stress events (increased intra-abdominal pressure), whereby the bladder pressure exceeds the urethral pressure. However, the closure function in healthy women is not yet fully understood, neither is the dysfunction in SUI patients. Our incomplete knowledge relates to the complexity of the closure apparatus and inadequate assessment methods (2).

The currently accepted view of the urethral closure function is based on the concept of a urethral sphincteric unit and a support system (2;3).

The sphincteric unit is the main contributor to the permanent closure forces which express the urethral pressure during the resting state (where the abdominal pressure is at its resting value where no voiding and no pelvic floor contraction occurs) (2).

The support system is thought to be the main contributor to the adjunctive closure forces superposed during stress events thus increasing the urethral pressure when the abdominal pressure increases (2;4). As long as the urethral pressure exceeds the abdominal pressure urinary leakage is prevented. Other factors of importance to the closure function are the urethral inner softness, the urethral deformability and the sensory function (4;5).

The sphincteric unit has traditionally been assessed by urethral pressure measurements at one point or at several points along the urethra forming the urethral pressure profile (UPP).

The support system has been assessed by the degree of bladder-neck or urethral mobility during stress events measured by the Q-tip test, ultrasound, video-cysto-urethrography and magnetic resonance imaging (MRI) (6;7).

The urethral deformability, the inner softness, and the sensory function have not been conceptualized into measurable parameters.

Due to artifacts and lack of standardization, the conventional methods for assessing the sphincteric unit and the support system have been unable to separate continent and SUI women or measure the severity of the disease. Consequently, we have no reliable clinical parameters for qualitative or quantitative purposes or to detect changes after intervention (8-11).

THE URETHRAL PRESSURE REFLECTOMETRY (UPR)

The urethral pressure reflectometry (UPR) is a method for simultaneous measurement of pressure and cross-sectional area (CA) in the urethra (12). It meets the requirements needed for investigation of pressure in a collapsible tube such as the urethra (13) as only a thin, small, light and flexible polyurethane bag that does not distend or straighten the urethra is inserted. Measurements are not affected by urethral movement; thereby artifacts due to catheter or transducer displacement are eliminated. Hence, UPR circumvents the problems encountered with conventional methods.

The obtained parameters are the urethral opening pressure (the pressure needed to just open the collapsed urethra (13)), the closing pressure, the opening and closing elastance, and the hysteresis, which are sound physical parameters that have previously shown to be of qualitative and quantitative value (12;14). These parameters can be obtained while resting or squeezing, in the supine and erect positions, with high accuracy and test retest reproducibility (15).

OBJECTIVES

MAIN OBJECTIVE

To investigate the urethral closure function by means of the UPR technique in SUI and continent women while resting and during intra-abdominal pressure increase, and to assess if the Tension-free Vaginal Tape (TVT) operation induces significant changes.

SPECIFIC OBJECTIVES

The main objective was subdivided into the following specific objectives:

- To investigate if the UPR parameters while resting and squeezing change after TVT (study I)
- To develop the UPR technique to allow fast measurements during intra-abdominal pressure increase (studies II and III)
- To assess the urethral closure function by means of the new UPR technique during intra-abdominal pressure increases by straining (pushing down) in SUI and continent women (study III)
- To investigate if the new UPR parameters change after TVT (study IV)

MATERIALS AND METHODS

THE STUDY POPULATIONS

Study I and IV

Twenty-two women with bothersome urodynamically proven SUI scheduled for a TVT operation were consecutively recruited via the outpatient clinic.

Subjects were excluded if they had pelvic organ prolapse (POP) stage 2 or greater, previous surgery for SUI or POP, hysterectomy within the last year before enrolment, detrusor overactivity on filling cystometry, intake of anti-muscarinic drugs within the last 3 months, overt neurological diseases, signs of lower urinary tract infection on urine dipstick, or were pregnant.

Study II

25 SUI and 8 continent women were included. Inclusion criteria were: women on whom UPR had been performed by the step-wise technique and the continuous technique within the same session (in other studies). The participants were recruited via the outpatient clinic and a clinical trial website for investigation in previous studies.

Study III

SUI women

Twenty-six women with bothersome urodynamic proven SUI were recruited consecutively from the outpatient clinic. Exclusion criteria were the same as in study I and IV.

Continent women

Ten continent volunteers with a negative cough stress test and an International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) score of 0 were consecutively recruited via a clinical trial website.

METHODS

All methods and terminology conform to the recommendations of the International Continence Society (ICS) unless otherwise stated. The UPR technique is not described in the ICS standardization report.

In addition to the UPR measurements, the pre- and postoperative assessment in study I and IV, and the assessment in study III included comprehensive medical history, ICIQ-SF, pelvic examination, filling cystometry, uroflowmetry, post-void residual urine measurement, cough stress test, urine analysis, pad-weighing test (2 x 24 hours), bladder diary (2 days), incontinence episode diary (7 days), ultrasound assessment and UPR measurements.

ICIQ-SF: This validated questionnaire was used to assess SUI severity and impact on quality of life, and to detect alterations after TVT operation. Minimal overall score is 0 and maximum 21.

Filling cystometry (Duet Logic, Mediwatch, Rugby, UK or MMS Solar Gold, MEQ, Enschede, the Netherlands) was undertaken using two 5 F transurethral catheters, one for filling the bladder and one for pressure measurements, and a fluid filled rectal catheter for estimation of abdominal pressure. With the patient seated, saline was infused at a medium filling rate (50 ml/min), and the diagnosis of urodynamic stress incontinence was based on the detection of urinary leakage while coughing in the absence of detrusor activity.

Uroflowmetry (Urodyn 1000, Mediwatch, Rugby, UK) was carried out in full privacy with the patient having “a normal desire to void”.

PVR was measured immediately after the micturition using a bladder scanner (Verathon Bladder Scanner BVI 9400, Bothell, WA, USA).

Cough stress test (five forceful coughs) was carried out in the standing position after inserting 150 ml of saline into the bladder via a catheter (10F).

The 2-day bladder diary included records of incontinence episodes, liquid intake, the times of micturitions and voided volumes.

In the 7-day incontinence diary the patient noted every incontinence episode in seven consecutive days.

3D and 4D perineal ultrasound (Voluson E8, GE Medical Systems, Zipf, Austria) was used as biofeedback to ensure strain without voluntary contraction of the pelvic floor muscles.

The TVT procedure (Gynecare, Division of Ethicon and Johnson & Johnson, Somerville, NJ, USA) was carried out using the technique described by Ulmsten et al. (16) under local anesthesia, with no concomitant surgical procedures.

UPR MEASUREMENTS

UPR methodology and equipment; the step-wise technique

UPR has previously been described in details (12). The equipment consists of an empty, thin, distensible polyurethane bag placed in the urethra and connected to a pump and an acoustic transmitter via a PVC tube. The polyurethane bag is inflated by pumping air into it, thereby increasing the pressure and distending the bag. The CA within the bag, and thus the urethra, can then be measured with acoustic reflectometry. Minimal measureable CA is 0.4 mm² and maximum CA is approximately 16 mm². Pressure within the bag can be applied and measured from 0 to 200 cm H_2O.

The patient was placed in the supine (lithotomic) position, and the bladder was emptied with a catheter (10F). The UPR polyurethane bag was placed in the urethra using a Ch. 5 baby feeding tube as guide wire, and the PVC tube was anchored to the urethral meatus using Duroderm® plaster. To ensure correct placement of the bag, it was inflated and deflated.

Measurements were conducted while resting and squeezing, in the supine (lithotomic) position and thereafter in the standing position. All measurements were conducted twice and the average of each parameter calculated for use as a study result.

Measurement while resting
The woman was instructed to relax during the measurements. Using the pump, the pressure was raised in steps of 5 cm H_2O from 0 cm H_2O and until the bag was completely open (Figure 2). The pressure was then decreased in steps of 5 cm H_2O until 0 cm H_2O. Each pressure step lasted 3 seconds, during which CA measurements within the bag were recorded. The whole procedure was repeated after a 15 sec pause.

Figure 1: The UPR measurement

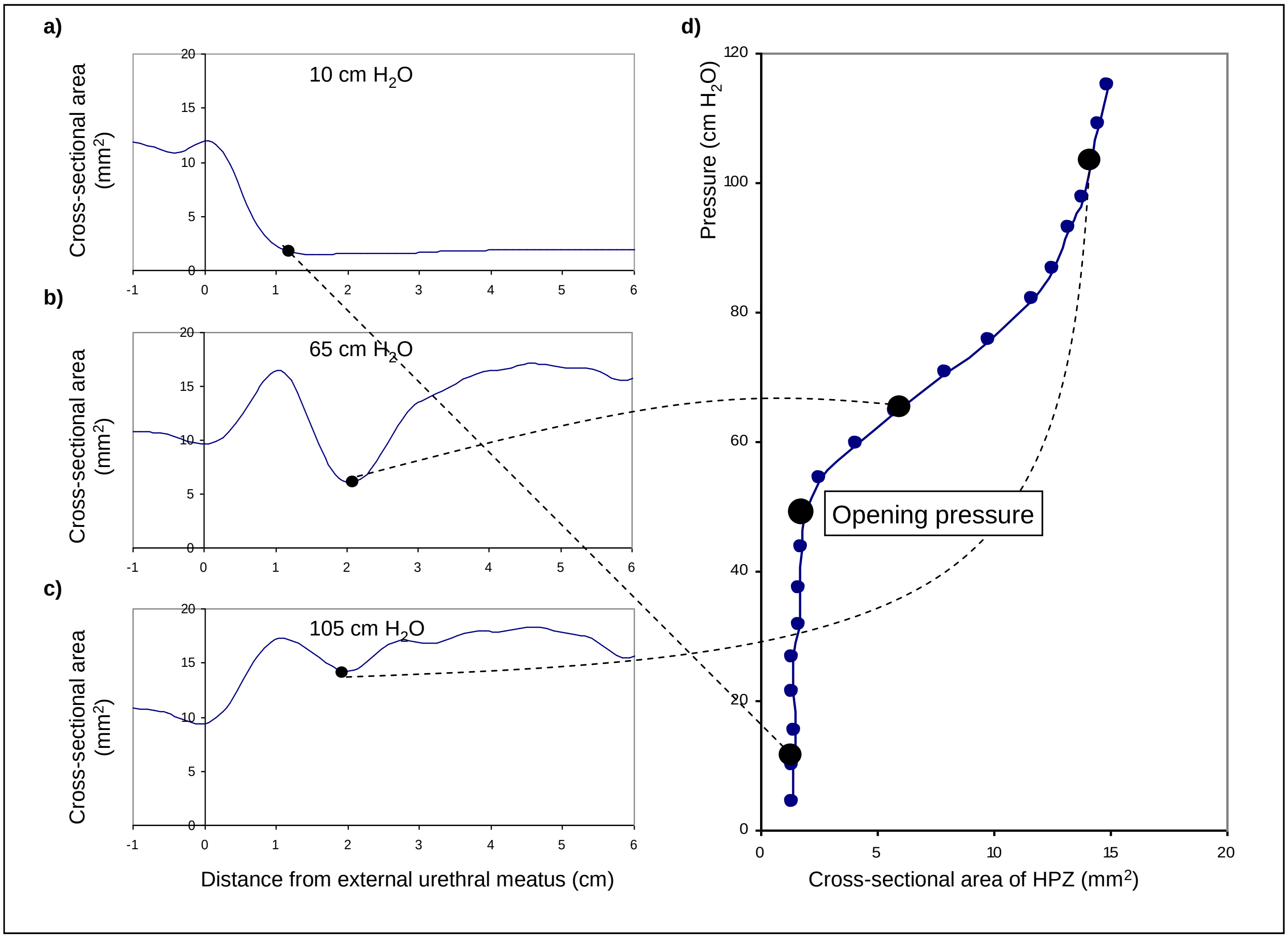

Figure 1 a–d: Measurement of a stress urinary incontinent woman while resting in the supine position.
1 a–c: the distance in centimeters on the x-axis is the distance along the length of the bag and thus the urethra. The high-pressure zone is seen as the point of minimal cross-sectional area at any given pressure, here shown at three different pressure levels: 10, 65 and 105 cm H_2O. This represents the component of the urethral closure function producing the greatest pressure on attempting to resist opening of the urethra. The minimal cross-sectional area values at each pressure level were plotted on a graph shown in 1 d.
HPZ: high-pressure zone

Measurement while squeezing

The woman was instructed on how to squeeze i.e., voluntary contraction of the pelvic floor without use of the abdominal muscles, and it was ensured that she squeezed correctly. Measurements were conducted with pressure steps of 10 cm H_2O until the bag was completely open, and the patient was asked to squeeze at each pressure plateau and to relax in the pauses when the pressure in the bag increased to the next pressure plateau (Figure 3 A). Squeezing measurements were conducted only while inflating the bag. The whole procedure was repeated after a 15 sec pause.

UPR parameters

The CA was measured at every millimeter along the length of the bag, producing 10 CA profiles per second. At each pressure-step, one mean curve was produced. Profiles at three different pressure levels are displayed in Figure 1 a–c. We only evaluated measurements from the high-pressure zone (HPZ) of the urethra, defined as the position in the urethra where the CA was smallest at a given pressure. The HPZ CA at each pressure level was plotted on a graph shown in Figure 1 d.

Figure 2 shows a pressure/CA graph with two traces: one during increasing pressure (inflation of the polyurethane bag) and one during decreasing pressure (deflation of the bag). The graph shows the opening pressure (P_o), the closing pressure (P_c), the opening and closing elastance and the hysteresis. The five parameters are defined in the figure.

During squeezing, only P_o and opening elastance were measured.

Figure 2: The UPR parameters

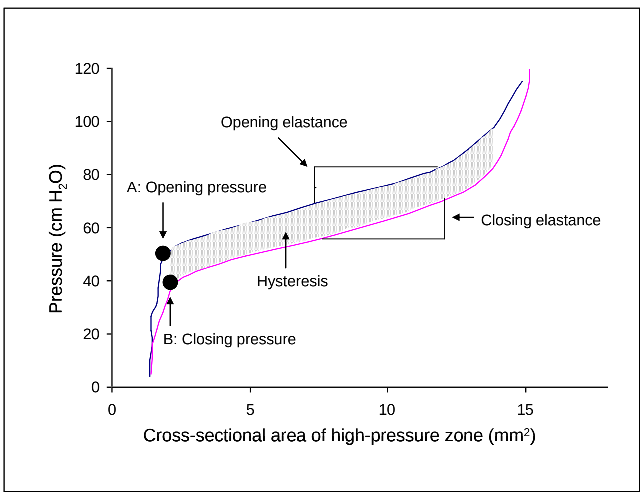

Figure 2: A UPR measurement and the obtained parameters. The cross-sectional area is that recorded within the bag at the high-pressure zone. The upper curve is produced while inflating the polyurethane bag and the lower while deflating the bag. Five parameters are obtained from the curves:

Opening pressure: The bag is initially closed. Increasing pressure does not result in increasing cross-sectional area until the pressure reaches the level at which the urethra is unable to resist opening: the opening pressure, point A.

Opening elastance: The cross-sectional area of the bag increases with increasing pressure along the curve from point A. The gradient of the curve represents the opening elastance (cm H2O/mm2), which reflects the resistance of the urethra to dilate in response to increasing pressure.

Closing elastance: The cross-sectional area of the bag decreases as the pressure decreases. The gradient of this curve represents the closing elastance, which is the ability of the urethra to close against a pressure.

Closing pressure: Minimal change in the area within the bag occurs after point B with decreasing pressure. The bag and urethra are now closed, recorded as closing pressure.

Hysteresis: This represents the amount of energy dissipated during the inflation and deflation of the bag (dilation and collapse of urethra), which is the difference between the area under the increasing curve and decreasing curve, respectively. It is given as the percentage compared with the increasing curve.

Modification of the UPR technique

When the pump that controls the pressure in the polyurethane bag is active the noise from the pump may interfere with the acoustic reflectometry measurements. The examination has therefore been made step-wise, which implies that the CA in the bag was measured at a given pressure level, then the pressure was increased to a new level and the CA was measured once again as described above. Such an examination takes at least 90 seconds which is longer than most women can squeeze or strain. Therefore, to measure during squeezing and straining, the squeeze or strain has to be repeated at each pressure level (Figure 3 A). This may lead to inaccuracy as the squeeze or strain may be of different strength each time and the woman may be fatigued.

A full measurement can be completed during only one squeeze or strain if the CA is measured during a continuous pressure change in the polyurethane bag (Figure 3 B).

The UPR technique has been modified so that measurements can now be performed within a time span of seven seconds, hence, measurements during pressure changes are possible. This new “fast” technique is designated “the continuous technique”.

UPR methodology and equipment; the continuous (“fast”) technique

The equipment consists of a computer with an integrated pressure recorder which is connected to a probe (containing an acoustic transmitter and a microphone), a 12 ml syringe and a polyurethane bag via a PVC tube.

With the woman supine the UPR polyurethane bag was inserted in the urethra as described above. Via the syringe air was pumped into the bag thereby increasing the pressure and distending the bag. The syringe was handled by hand. The CA along the length of the bag, and thus the urethra, was measured continuously with acoustic reflectometry, and the P_o was obtained.

Measurements were conducted while resting and during increased intra-abdominal pressure by straining in the supine position.

The abdominal pressure (P_{Abd}) was continuously measured with an air filled balloon catheter (T-dock, Wenonah, NJ, USA) in the rectum.

Measurements while resting

The woman was instructed to relax during the measurements. The pressure in the bag was increased from 0 cm H_2O to 200 cm H_2O within seven seconds by pressing the piston steadily down and decreased by pulling the piston back again within seven seconds, and the resting urethral opening pressure ($P_{o\text{-}rest}$) was recorded.

Figure 3: The step-wise technique and the continuous technique

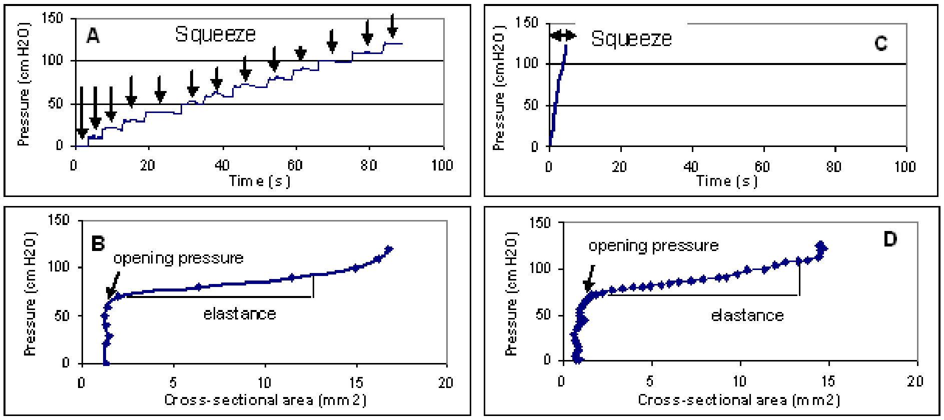

Figure 3: A shows the pressure inside the polyurethane bag during squeezing using the step-wise technique. The subject squeezes at each pressure level (indicated with an arrow). B shows the pressure and the corresponding minimum cross-sectional area from the squeezing measurement in A. The opening pressure and elastance (slope of the curve) are indicated. C shows a squeezing measurement using the continuous ("fast") technique. The subject holds the squeeze during the pressure increase in the polyurethane bag. D shows the pressure and the corresponding minimum cross-sectional area measured with the continuous technique.

Figure 4: UPR measurements during intra-abdominal pressure increase

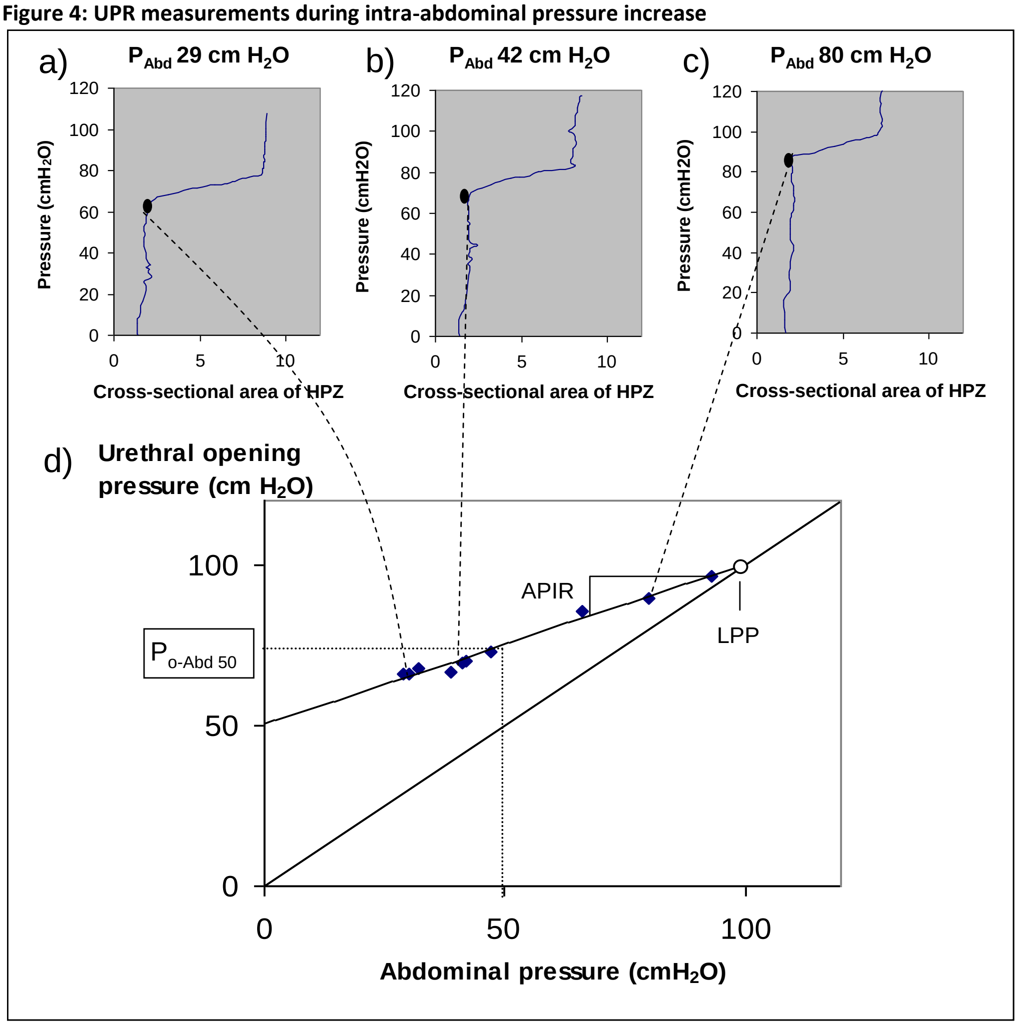

Figure 4 a-c: UPR measurements from an SUI woman obtained at three different levels of intra abdominal pressure. The opening pressures are marked with dots. 4 d: Pressuregram with opening pressures obtained from 10 measurements at different levels of increased intra-abdominal pressure, including the opening pressures from the Figures 4 a-c. The linear regression line of the data was conducted and APIR (slope of the line) and intercept with the y-axis were found. The HPZ pressuregram-LPP is defined as the intercept with the equilibrium line of x=y and can be read from the pressuregram or calculated. The urethral opening pressure at 50 cm H_2O abdominal pressure ($P_{o\text{-}Abd\ 50}$) is indicated

UPR: Urethral pressure reflectometry, HPZ: High-pressure zone, APIR: Abdominal to urethral Pressure Impact Ratio, LPP: leak point pressure.

Measurements during increased intra-abdominal pressure
The woman was instructed to increase the abdominal pressure by straining (pushing down) 10 times at different intensities (to obtain measurements at a broad spectrum of abdominal pressures) and keep the pressure for at least seven seconds. At each strain the pressure in the bag was increased from 0 cm H_2O to 200 cm H_2O within seven seconds and decreased again within seven seconds. The P_o and the simultaneous P_{Abd} (by the T-dock catheter in the rectum) were recorded.

The UPR parameters obtained by the continuous technique
The related values of P_o and P_{Abd} at the 10 different abdominal pressures were plotted into a HPZ abdomino-urethral pressuregram (Figure 4). Linear regression of the values was conducted, and the slope of the line and the intercept with the y-axis estimated (17).

The slope expresses the effect of the abdominal pressure increase on the urethral pressure and is designated "Abdominal to urethra Pressure Impact Ratio" or "APIR". The $\text{intercept}_{\text{y-axis}}$ is a mere mathematical parameter as the clinical abdominal pressure will never be 0 cm H_2O.
The equation of the HPZ pressuregram line:

$$P_o = (\text{APIR} \times P_{Abd}) + \text{intercept}_{\text{y-axis}}$$

was used to calculate P_o at specific values of P_{Abd}, e.g., 50 cm H_2O: $P_{\text{o-Abd 50}}$ (Figure 4).

The HPZ pressuregram-leak point pressure (pressuregram-LPP), which is defined as the intercept with the equilibrium line of x=y (Figure 4) could be calculated from the equation:

$$\text{HPZ pressuregram-LPP} = \text{intercept}_{\text{y-axis}} / (1 - \text{APIR})$$

(from Kim et al (17))

An APIR < 1 implies that the pressuregram line intercepts the equilibrium line and that the HPZ pressuregram-LPP can be calculated. An APIR ≥ 1 implies that the pressuregram line does not intercept the equilibrium line at increasing abdominal pressure; the HPZ pressuregram-LPP is "infinite".

DEFINITION OF CLINICAL OUTCOME

Studies I and IV

Subjective cure: no reported incontinence on ICIQ-SF, improvement: ≥ 50% decrease in post-operative ICIQ-SF score (compared to pre-operative score), and failure: < 50% decrease in post-operative score.

Objective cure: negative stress test and < 5 g leakage at the pad test, improvement: a negative stress test and ≥ 5 g leakage at the pad test, and failure: leakage at stress test.

STATISTICAL CONSIDERATIONS

Power calculations

Study I
Before the study, power calculations showed that 11 patients were needed (power: 90%, two sided P-value 0.05) for the relaxing P_o for the statistical test to detect a difference after surgery, with the assumption of a clinically relevant increase of 5 cm H_2O in the resting opening pressure. For the squeezing opening pressure, 19 patients were needed, assuming a clinically relevant change in the squeezing P_o to be 5 cm H_2O (power: 90%, two sided P-value 0.05).

Study IV
Before the study, power calculations showed that 21 patients were needed (power: 90 %, two sided P-value 0.05) to detect a 10 % difference in APIR.

No power calculations were performed before study II and III.

Statistical methods

Studies I and IV
Data were tested with the paired t-test on Microsoft Excel software and presented as mean and standard deviation. A p value ≤ 0.05 was used to define significance in statistical comparisons.

Study II
The coefficient of variance (CV) was calculated as the standard deviation (SD) divided by the mean. The CV was presented in percent.

Studies III and IV
Linear regression of abdominal and urethral pressure data was conducted using the Microsoft Excel software (2007, Microsoft, Redmond, WA, USA).

Study III
Data were tested by the Mann-Whitney U test and presented as median and range (due to the small sample sizes). Correlations between parameters were tested with Spearman's test. The Statistical Package for Social Sciences version 19 (SPSS 19, IBM, Armonk, NY, USA) was used. Confidence intervals for specificity and sensitivity of the Urethral Closure Equation were calculated using an exact binomial method using R ver. 2.14.1 (open source statistical program available from Comprehensive R Archive Network (CRAN)). Statistical significance was determined at p ≤ 0.05.

ETHICS
The study was approved by The Committees on Biomedical Research Ethics for the Capital Region of Denmark (H-B-2008-002), and informed consent was obtained from all participants.

RESULTS

STUDY I. UPR BY THE STEP-WISE TECHNIQUE BEFORE AND AFTER TVT

Patient characteristics are listed in Table 1. All patients had delivered vaginally only, except one who had had no vaginal deliveries but one caesarean section.

Table 1: Demographic characteristics

n = 22	**Median**	**Range**
Age (years)	54	38—68
Parity	2	1—3
Weight (kg)	77	52—100
Height (cm)	168	153—178
BMI (kg/m^2)	28	19—36

BMI: Body Mass Index

Median follow-up time was 160 days (range: 84–401 days). The subjective cure rate was 82% (18/22), the improvement rate 18% (4/22) and the failure rate 0%. The four improved patients all reported "leakage before reaching the toilet" (0-2 leakage episodes per week) interpreted as de novo urge. Objectively, 100% were cured. The number of incontinence episodes (24h), ICIQ-SF-score, stress test and pad test all changed significantly after surgery (Table 2). The mean maximum urine flow rate decreased from 31 to 18 ml/sec after surgery (p=0.0002) and the mean PVR increased from 12 to 24 ml (p=0.057).

There was no difference in demographic characteristics or incontinence severity before surgery between cured and improved patients.

The UPR parameters are presented in Table 3.

In the supine position, we found no change in the resting P_o or P_c after TVT. There was an 18% increase in the opening and closing elastance, respectively, with the patient resting. The hysteresis was unchanged after surgery.

The supine squeezing P_o decreased 6 cm H_2O (10%) after surgery, with no difference between cured and improved patients. The supine squeezing opening elastance was unchanged after TVT.

In the standing position, the P_o and P_c and the opening elastance were unchanged, whereas the closing elastance increased by 11%. The hysteresis was unchanged.
The squeezing P_o and elastance did not change in the standing position after surgery.

Table 2: Clinical outcome measures

n = 22	**Before TVT**	**After TVT**	**p-value**
Incontinence (number of episodes/24h)	3.23	0.06	<0.0001
ICIQ-SF (score)	14.64	1.09	<0.0001
Positive stress test (n)	22	0	<0.0001
Pad test (g/24h)	43	0,1	<0.0001
Maximum urine flow rate (ml/sec)	31	18	0.0002
Post-Void Residual urine volume (PVR) (ml)	12	24	0.057
Weight (kg)	77	76,3	0.48

Mean values. ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form.

Table 3: UPR parameters before and after TVT

n = 22		**Before TVT**	**After TVT**	**p-value**
Supine resting	opening pressure (cm H_2O)	46 (11)	44 (10)	0.2
	closing pressure (cm H_2O)	36 (8)	35 (8)	0.4
	opening elastance (cm H_2O/mm^2)	1.6 (0.5)	1.9 (0.6)	0.04
	closing elastance (cm H_2O/mm^2)	1.5 (0.4)	1.8 (0.4)	0.01
	hysteresis (%)	19 (8)	19 (5)	0.8
Supine squeezing	opening pressure (cm H_2O)	58 (14)	52 (11)	0.01
	opening elastance (cm H_2O/mm^2)	1.7 (0.6)	1.9 (0.7)	0.4
Standing resting	opening pressure (cm H_2O)	72 (14)	74 (12)	0.5
	closing pressure (cm H_2O)	62 (13)	63 (12)	0.3
	opening elastance (cm H_2O/mm^2)	1.9 (0.5)	2.0 (0.5)	0.3
	closing elastance (cm H_2O/mm^2)	1.8 (0.5)	2.0 (0.4)	0.05
	hysteresis (%)	13 (6)	12 (5)	0.4
Standing squeezing	opening pressure (cm H_2O)	81 (14)	80 (13)	0.6
	opening elastance (cm H_2O/mm^2)	1.9 (0.7)	2.2 (0.7)	0.1

Mean (SD). UPR: Urethral Pressure Reflectometry. TVT: Tension-free Vaginal Tape

STUDY II. THE UPR CONTINUOUS TECHNIQUE COMPARED WITH THE STEP-WISE TECHNIQUE

Measurements by the continuous method were well tolerated by the women, easy to perform and could be conducted while resting and straining within 15 minutes all together.

The mean squeezing P_o was 67 cm H_2O by the continuous technique and 64 cm H_2O by the step-wise technique, the difference was not significant (p=0.07). The mean squeezing opening elastance was significantly higher with the continuous technique compared to the step-wise technique. The CV of the squeezing P_o was 6.5% while the CV of the squeezing opening elastance was 14.8%.

STUDY III. UPR DURING INTRA-ABDOMINAL PRESSURE INCREASE IN SUI AND CONTINENT WOMEN

Three women were excluded for various reasons; hence 25 SUI patients and 8 continent volunteers were included in the analyses. The two groups did not differ with respect to age, Body Mass Index or menopausal status, but the SUI women had had more vaginal deliveries (Table 4).

The median $P_{o\text{-}rest}$ appears from Table 5. All SUI women had a $P_{o\text{-}rest} \leq 58$ cm H_2O, while the continent women had $P_{o\text{-}rest}$ between 43 cm H_2O and 95 cm H_2O.

The median APIR was 0.72 in SUI women and 1.05 in continent women (p=0.002), but the APIR did not separate SUI and continent women (Table 5). The APIR expresses the effect of the P_{Abd} increase on the urethral P_o.

Of the SUI women, 23 had an APIR < 1 during abdominal pressure increase by strain and their median HPZ pressuregram-LPP was 100 cm H_2O (range 36-580 cm H_2O). The remaining two SUI women had an APIR > 1 resulting in an infinite HPZ pressuregram-LPP.

In 6 of the continent women the APIR was ≥ 1 resulting in an infinite HPZ pressuregram-LPP. The APIR was < 1 in the remaining two continent women resulting in HPZ pressuregram-LPP of 185 cm H_2O and 840 cm H_2O, respectively.

The median $P_{o\text{-}Abd\ 50}$ was 67 cm H_2O in SUI women versus 104 cm H_2O in continent women (p<0.0005) (Table 5). This parameter completely separated the two groups of women (Figure 5). The urethral P_o at abdominal pressures of 0, 100, 150, 200 and 250 cm H_2O were also calculated and showed significant differences between SUI and continent women.

When the $P_{o\text{-}rest}$ and the APIR were plotted into a scattergram the SUI women appeared in the lower left part of the scattergram while the continent women appeared in the upper right part (Figure 6). A line could be drawn that separated SUI and continent women. The equation of the line was found; the Urethral Closure Equation (UCE) line:

$$(2 * p * \text{square root } ((0.02* P_{o\text{-}rest})^2 + (1.2 * APIR)^2 * 0.5)) – 7.15$$

Sensitivity: 1 (Confidence interval: 0.86-1.0), specificity: 1 (Confidence interval: 0.63-1.0).

SUI women in the study all had negative results when inserting their values into the UCE, while all continent women had positive results.

Table 4: Baseline characteristics

	SUI (n = 25)	Continent (n = 8)	p-value
Age (years)	53 [38 - 68]	50 [37 - 65]	0.12
BMI	27 [19 - 36]	28 [20 - 35]	0.69
Para, total	2 [1 - 3]	1 [0 - 2]	0.018
Vaginal deliveries	2 [0 - 3]	1 [0 - 2]	0.012
Caesarean sections	0 [0 - 1]	0 [0 - 2]	0.79
Post menopausal (per cent)	52%	50%	
Topic estrogen treatment (per cent)	20%	0%	
ICIQ-SF score	15 [10 - 18]	0 [0 - 0]	<0.0005

Mann-Whitney U test. Median [range]. BMI: Body Mass Index. ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form.

Table 5: UPR measures while resting and during increased intra-abdominal pressure

	SUI (n = 25)	Continent (n = 8)	p-value
$P_{o\text{-}rest}$ (cm H_2O)	40 [24 - 58]	68 [43 - 95]	<0.0005
APIR*	0.72 [0.35 - 1.05]	1.05 [0.46 - 1.31]	0.002
$P_{o\text{-}Abd\ 50}$ (cm H_2O)*	67 [46 - 83]	104 [85 - 151]	<0.0005
Urethral Closure Equation*	-1.82 [-3.50 - - 0.05]	1.18 [0.32 - 2.98]	<0.0005

Median [range] by Mann-Whitney U test. SUI: Stress Urinary Incontinent, $P_{o\text{-}rest}$: Urethral opening pressure while resting, APIR: Abdominal to urethra Pressure Impact Ratio. $P_{o\text{-}Abd\ 50}$: Urethral opening pressure at 50 cm H_2O abdominal pressure. *obtained by use of the pressuregram.

The correlations between $P_{o\text{-}rest}$, APIR, $P_{o\text{-}Abd\ 50}$ and the UCE results, and the clinical measures of ICIQ-SF, pad test and number of incontinence episodes per week were calculated (pooled data of continent and SUI women) (Table 6). $P_{o\text{-}rest}$ showed significant moderate negative correlation with pad test and number of incontinence episodes per week. $P_{o\text{-}Abd\ 50}$ and the UCE results showed highly significant strong negative correlation with ICIQ-SF, pad test and number of incontinence episodes per week.

Calculation of the receiver operating characteristic (ROC) curves showed the area below the curve (AUC) to be 1.0 for the measures $P_{o\text{-}Abd\ 50}$ to $P_{o\text{-}Abd\ 100}$, and for the UCE results.

Correlation tests on the pooled data showed that $P_{o\text{-}rest}$ significantly decreased with age (controlled for total number of deliveries) (r= -0.35, p=0.05) and with total number of deliveries (controlled for age) (r=-0.61, p<0.0005).

APIR did not correlate with age (controlled for total number of deliveries) (r=-0.01, p=0.98) and was not demonstrated to significantly decrease with total number of deliveries (controlled for age) (r=-0.272, p=0.13).

Figure 5: UPR parameters in SUI and continent women

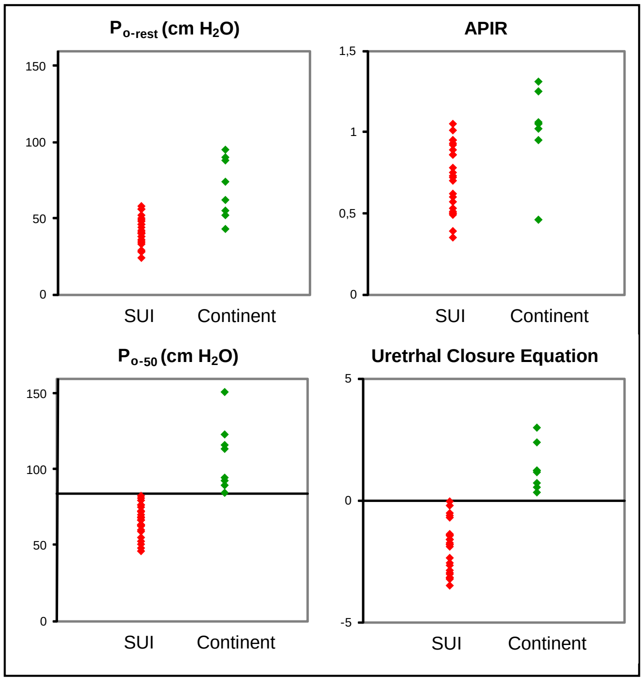

Figure 5: $P_{o\text{-}rest}$, APIR, $P_{o\text{-}Abd\ 50}$ and the Urethral Closure Equation result in SUI and continent women. SUI: stress urinary incontinent, $P_{o\text{-}rest}$: urethral opening pressure while resting, APIR: Abdominal Pressure Impact Ratio, $P_{o\text{-}Abd\ 50}$: Urethral opening pressure at 50 cm H_2O abdominal pressure.

Figure 6: Scattergram of resting urethral opening pressure and APIR

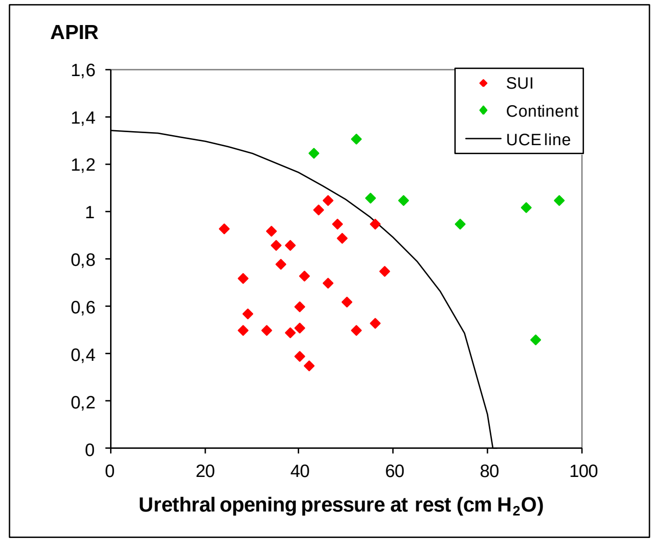

Figure 6: Scattergram of resting urethral opening pressure and APIR. Women in the lower left part of the scattergram (below the line) are likely to be SUI, while women in the upper right part (above the line) are likely to be continent. APIR: Abdominal to urethra Pressure Impact Ratio. SUI: Stress Urinary Incontinent. UCE: Urethral Closure Equation.

Table 6: Correlation between UPR measures and ICIQ-SF, pad test and number of incontinence episodes per week

n = 33	ICIQ-SF score	Pad test	Incontinence episodes per week
$P_{o\text{-}rest}$ (cm H_2O)	-0.324	-0.434*	-0.437*
APIR	-0.310	0.008	-0.317
$P_{o\text{-}Abd\ 50}$ (cm H_2O)	-0.563**	-0.527**	-0.528**
Urethral Closure Equation	-0.455**	-0.361*	-0.521**

Correlation coefficients by Spearman's test. $P_{o\text{-}rest}$: urethral opening pressure while resting. APIR: Abdominal Pressure Impact Ratio, $P_{o\text{-}Abd\ 50}$: Urethral opening pressure at 50 cm H_2O abdominal pressure, ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form
**: Correlation significant at the 0.01 level. *: Correlation significant at the 0.05 level

STUDY IV. UPR DURING INTRA-ABDOMINAL PRESSURE INCREASE BEFORE AND AFTER TVT

The 22 women included were the same as included in Study I. One subject was excluded from analysis due to insufficient UPR tracing. Median age of the remaining 21 women was 54 years (range 38-69 years), median parity was 2 (range 1-3), and median Body Mass Index was 28 (range 20-36).

The subjective cure rate after TVT operation was 81% (17/21), the improvement rate 19% (4/21) and the failure rate 0%. The 4 improved patients all reported "leakage before reaching the toilet" (0-2 leakage episodes per week) which was interpreted as de novo urge. Objectively, 100% were cured. ICIQ-SF-score, pad test, and number of incontinence episodes per week all decreased significantly after TVT.

The UPR results are presented in Table 7 and Figure 7.

APIR increased in all subjects, and mean APIR increased from 0.70 to 1.37 ($p<0.0001$). Mean $P_{o\text{-}Abd\ 50}$ increased from 66 to 85 cm H_2O after TVT and mean $P_{o\text{-}Abd\ 100}$ increased from 103 to 154.

When inserting $P_{o\text{-}rest}$ and APIR into the UCE the result was negative in all patients before TVT. After TVT the UCE result had increased in all patients, with a mean increase of 2.96. The result increased to a positive value in 15 of the 21 patients. This was also reflected in the scattergram of $P_{o\text{-}rest}$ and APIR where all patients moved upwards after TVT (Figure 8).

Preoperative $P_{o\text{-}rest}$ and APIR, respectively, did not differ among cured and improved patients.

Table 7: UPR outcome measures

n = 21	Before TVT	After TVT	p-value
$P_{o\text{-}rest}$ (cm H_2O)	42.3 (8.2)	42.6 (8.6)	0.77
APIR	0.70 (0.21)	1.37 (0.43)	<0.0001
$P_{o\text{-}Abd\ 50}$ (cm H_2O)	66.3 (9.6)	85.4 (18.4)	0.0001
$P_{o\text{-}Abd\ 100}$ (cm H_2O)	101.3 (21.4)	153.9 (39.3)	<0.0001
UCE	-1.79 (1.06)	1.16 (2.09)	<0.0001

Mean (Standard Deviation). UPR: Urethral Pressure Reflectometry, TVT: Tension-free Vaginal Tape, $P_{o\text{-}rest}$: Resting urethral opening pressure, APIR: Abdominal to urethra Pressure Impact Ratio, $P_{o\text{-}Abd\ 50}$: Urethral opening pressure at 50 cm H_2O abdominal pressure, $P_{o\text{-}Abd\ 100}$: Urethral opening pressure at 100 cm H_2O abdominal pressure, UCE: Urethral Closure Equation.

Figure 7: UPR outcome measures before and after TVT

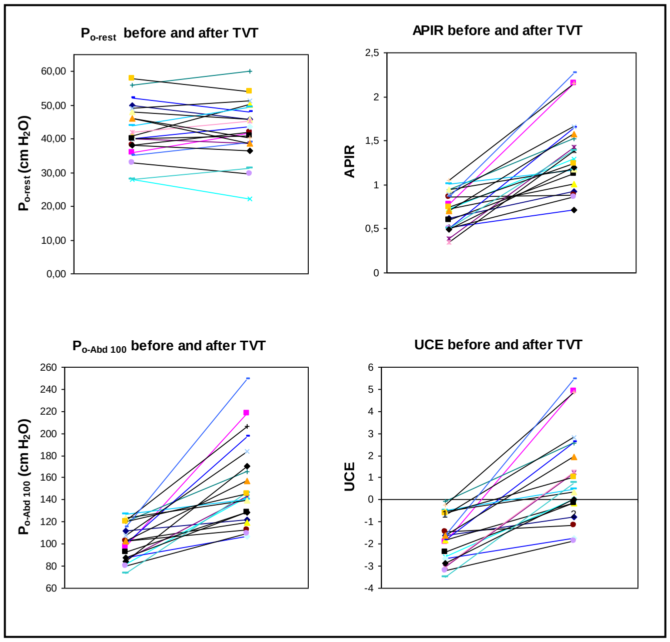

Figure 7: $P_{o\text{-}rest}$, APIR, $P_{o\text{-}Abd\ 100}$ and UCE before and after TVT.
TVT: Tension-free Vaginal Tape, $P_{o\text{-}rest}$: urethral opening pressure while resting, APIR: Abdominal to urethra Pressure Impact Ratio, $P_{o\text{-}Abd\ 100}$: Urethral opening pressure at 100 cm H_2O abdominal pressure, UCE: Urethral Closure Equation.

Figure 8: Scattergram of APIR and resting urethral opening pressure

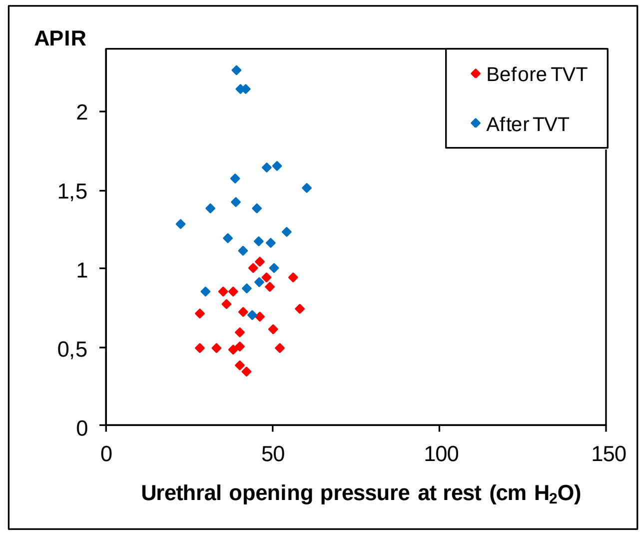

Figure 8: Scattergram of $P_{o\text{-}rest}$ and APIR before and TVT.
$P_{o\text{-}rest}$: Urethral opening pressure while resting, APIR: Abdominal to urethra Pressure Impact Ratio, TVT: Tension-free Vaginal Tape

DISCUSSION

The UPR technique has shown promising results when measurements are performed during resting and squeezing (12). In this PhD study the technique has been further developed to allow measurements during intra-abdominal pressure increase. Thus the studies were conducted partly by the traditional UPR technique and partly by the new ("fast") technique and have resulted in new urethral parameters, which have gained new insight into the urethral closure function.

The urethral sphincteric unit as measured by the resting urethral pressure has been suggested to represent the permanent closure forces of the urethral closure function (4). UPR measurements showed a statistically significant difference between a $P_{o\text{-}rest}$ of 40 cm H_2O in SUI women and 68 cm H_2O in continent women. This is in accordance with data from Klarskov et al who found a $P_{o\text{-}rest}$ of 40 cm H_2O in SUI women and 72 cm H_2O in continent women (14). Despite the improved (decreased) variability observed using the continuous technique it does not allow separation of SUI and continent women. Earlier reports of resting urethral pressure measurements using UPP have shown an average MUCP of 39 cm H_2O in SUI women and 54 cm H_2O in continent women (2), however, with large overlap between groups.

The support system has traditionally been assessed by the bladder-neck mobility or the mid-urethral mobility.

According to the bladder-neck theory, the urethra and the bladder neck are compressed against a supportive layer of structures extrinsic to the urethra, the "Hammock", during intra-abdominal pressure increase (18). A dysfunctional supportive layer with subsequent decreased resistance is supposed to cause bladder-neck hypermobility which is widely accepted to be associated with SUI (5;6).

According to the mid-urethral theory, the central urethral mobility rather than the bladder neck mobility is important to the continence function. Zacharin suggested "the suspensor mechanism" (a ligamentous complex including the pubo-urethral ligament) to limit the mid-urethral mobility by acting as a central fulcrum between the bladder and the external urethral meatus (19). Hence, when the bladder descends caudally during intra-abdominal pressure increase the urethra is subsequently compressed at its mid-point. Recently, dysfunctional mid-urethral support and subsequent mid-urethral hypermobility has been reported to be strongly associated to SUI (20;21). Accordingly, dysfunctional mid-urethral support may cause insufficient mid-urethral pressure increase.

The present study indicates that the adjunctive closure forces, which include the urethral support (4), can be assessed by the APIR. APIR is defined as the slope of the HPZ pressuregram line and measures the impact of increase in P_{Abd} on the P_o. In all measurements the urethral HPZ was located at the mid-urethra. The finding of a median APIR of 0.72 in SUI women and 1.05 in continent women (p=0.002) confirms that the mid-urethral support and pressure is more important to the urethral closure function than the bladder neck.

The APIR values >1 cannot be due to mere compression of the urethra by neighboring structures; respecting the laws of physics only a mid-urethral kink as suggested by Zacharin (19) could induce such a high pressure increase (9). The exact anatomical basis of insufficient mid-urethral support and decreased APIR needs to be further investigated.

The urethral pressure increase during intra-abdominal pressure increase has in the literature been designated “pressure transmission ratio” (PTR) which is misleading as the urethral pressure is not transmitted from the abdomen, but builds up synchronously (9). The PTR has been reported for different parts of the urethra but never precisely for the HPZ. Some investigators have reported decreased values of mid-urethral PTR in SUI women compared to continent women (17;22), while other have found no difference (23).

The P_o at a given P_{Abd} represents the resulting effect of the permanent and adjunctive closure forces at that particular P_{Abd}. As an example $P_{o\text{-}Abd\ 50}$ differed significantly in SUI and continent women and revealed an impaired closure function in SUI women already at this relatively low abdominal pressure level. The difference was so pronounced that SUI and continent women were completely separated (Table 5 and Figure 5).

$P_{o\text{-}rest}$ and APIR plotted against each other in a scattergram showed complete visual separation of SUI and continent women and allowed us to determine the UCE line: a threshold below which SUI occurred. When entering a woman’s values of $P_{o\text{-}rest}$ and APIR into the UCE, a negative result indicates a weak urethral closure function pointing towards SUI while a positive result indicates a stronger closure function. Supposedly, there is a grey area around the UCE line where the presence of SUI is dependent on the abdominal pressure level a woman is subjected to.

From the scattergram and the UCE it appears that both $P_{o\text{-}rest}$ and APIR contribute to the urethral closure function, and that women with low values of both parameters are more likely to experience SUI than women with high values of both parameters. This is in accordance with previous reports of MUCP and urethral support being largely independent predictors of SUI (24). In this study, all SUI women had a $P_{o\text{-}rest}$ < 60 cm H_2O. The continent women who had a $P_{o\text{-}rest}$ < 60 cm H_2O had an APIR > 1 hence it seemed that women with only one low parameter were able to compensate and remain continent if the other parameter was proportionally high.

Therefore, we suggest that the urethral closure function can be characterized by means of $P_{o\text{-}rest}$ and APIR. The inner softness is included in $P_{o\text{-}rest}$, and the urethral deformability is included in the resulting P_o during intra-abdominal pressure increase and accordingly in the APIR. The elastance contributes to the resting closure function but is not comprised in the $P_{o\text{-}rest}$. We are aware that the urethral pressure represents the resultant contribution of a number of structures and hence provides no precise information of the origin of the pressure (25).

When looking at the ROC curve of P_o at abdominal pressures between 50 and 100 cm H_2O and of the UCE, respectively, we found the AUC to be 1, which indicates optimal performance as diagnostic tests (26). To our knowledge, these are the first urethral parameters demonstrating to be robust qualitative and quantitative clinical parameters usable as diagnostic tests in SUI women (2;8;10).

$P_{o\text{-}Abd\ 50}$, $P_{o\text{-}Abd\ 100}$ and the UCE results, respectively, showed stronger negative correlation with ICIQ-SF, pad test and number of incontinence episodes per week than did the $P_{o\text{-}rest}$, APIR, and earlier reported parameters obtained by conventional UPP method (8). $P_{o\text{-}Abd\ 50}$, $P_{o\text{-}Abd\ 100}$ and the UCE are therefore quantitative SUI parameters and can be used as SUI severity measures.

$P_{o\text{-}rest}$ was negatively correlated with age and number of deliveries, respectively, which is in agreement with the reported average MUCP decrease of 15 cm H_2O per decade (27;28). Therefore, in the course of time and additional deliveries, respectively, a woman will move towards the left of the scattergram of $P_{o\text{-}rest}$ and APIR (i.e. towards a weaker closure function). Hence, these parameters potentially may be used to predict the occurrence of SUI in a particular woman following increased age or additional deliveries.

APIR did not decrease with age and was not demonstrated to significantly decrease with number of deliveries. This is in accordance with recent reports that levator ani avulsion caused by deliveries does not seem to significantly influence the mid-urethral mobility (29). However, it contradicts the earlier suggested notion that the urethral support is decreased after vaginal delivery (28) and the commonly held opinion that levator avulsions are related to SUI.

The mechanism of action behind the effect of TVT remains virtually unknown, and there is no robust parameter that has proven to change after intervention. We investigated if the UPR parameters could be used for this purpose.

Mean supine $P_{o\text{-}rest}$ was unchanged after TVT (paper I and IV) which is consistent with previous reports of supine resting urethral pressure measurements (30-34) and with biomechanical statements (9). Additionally, we found that P_o was unchanged in the erect position, which to our knowledge is new information.

However, the supine opening elastance increased by 18% after TVT, which indicates that the TVT sling increases the resistance against dilation of the urethra and thus somewhat improves the closure function at the resting state. This increased resistance against opening, e.g., for urine flow, probably explains the decreased maximum urine flow rate observed after TVT placement in this study and in previous reports in the literature (35;36).

The hysteresis may reflect the urethral tissue fiber composition. Therefore, scar tissue formation with increased fibrosis after sling surgery (37) could increase hysteresis. In this study, the hysteresis was unchanged, indicating that the TVT had not induced major fibrosis. This is in accordance with previous reports of minimal inflammatory reaction at two-year follow-up after TVT operation (38).

APIR increased to levels of continent women (or higher) in all patients after TVT, which is in accordance with reports of decreased mid-urethral mobility after TVT (20;33;39-44). Hence, TVT may work by imitating the natural mid-urethral fixation (19) thereby enhancing the mid-urethral support with subsequent decreased mid-urethral mobility and increased P_o during stress.

The increase in APIR to values >1 is suggested to arise by the same mechanism as discussed previously: kinking of the urethra during stress. Mid-urethral kinking after TVT has been visualized by ultrasound and MRI in several studies (20;33;39-44).

Many investigators reported an increased PTR after TVT (31;33;45), while some did not (32;46). The heterogeneity of those results is not surprising as PTR has low reproducibility (3;10).

As TVT virtually only improved the APIR, women with a low pre-operative $P_{o\text{-}rest}$ did not restore the normal urethral closure mechanism but regained continence by an enhanced APIR which was then able to compensate for the low $P_{o\text{-}rest}$. This was visualized in the scattergram of related values of $P_{o\text{-}rest}$ and APIR before and after TVT (Figure 8) which revealed a mere upward movement of the values after TVT and not a diagonal movement towards the values of continent women (Figure 6).

$P_{o\text{-}Abd\ 100}$ increased in all patients, mean $P_{o\text{-}Abd\ 100}$ increased from 101 cm H_2O to 154 cm H_2O which is above the median value of 147 cm H_2O in continent women (results not shown).

Likewise, when inserting the parameters into the UCE, all patients achieved a stronger closure function after TVT. Not all patients exceeded the threshold value of a "normal" urethral closure function although they all re-gained continence.

With the presented results, we suggest to use the APIR, $P_{o\text{-}Abd\ 50}$, $P_{o\text{-}Abd\ 100}$ and UCE as parameters to objectify the urethral closure function changes after intervention.

Until now no parameter has demonstrated to be a robust predictor of TVT failure. Due to lack of failures and the small study population we could not clarify the role of $P_{o\text{-}rest}$ or APIR as predicting factors, however, it seems plausible that a certain low level of APIR may be predictive of a better effect of TVT than a high level.

The knowledge that urethral dysfunction is caused by a decreased $P_{o\text{-}rest}$ or APIR and that TVT is able to induce increased APIR may help gynecologists select the proper treatment for a specific patient; however studies are needed to determine other anti-incontinence treatments effect on the urethral closure function.

METHODOLOGICAL CONSIDERATIONS

The UPR method provides advantages compared to conventional urodynamic methods because of the thin and flexible polyurethane bag that allows bending of the urethra during measurements, the reduced risk of catheter-urethral wall interaction due to the luminal pressure measurements, and the measurements in the urethral HPZ.

Until now the pressure in the UPR polyurethane bag has been controlled by a pump with feedback from a pressure transducer. As CA measurements are affected by noise from the pump they could only be obtained during the breaks between the pressure-increases. The technique can be used while resting and squeezing but is inadequate when measuring the urethral opening pressure during stress events. We therefore modified the technique. By the UPR continuous technique, the pressure is increased by hand, hence minimal sound is generated, and measurements can be obtained continuously. This allows measurements during stress events.

Regardless of the technical differences between the step-wise and the continuous technique there was no statistical difference between the mean P_o while resting (results not shown) and while squeezing, measured by the two techniques. The squeezing opening elastance was significantly higher when obtained by the continuous technique compared to the step-wise technique. Therefore, when the elastance is provided, it is important to describe the method by which it is measured. The reproducibility of the continuous technique is somewhat better than previously described for the step-wise technique (squeezing P_o CV of 6.5% vs. 8.5% for the continuous technique and step-wise technique, respectively (15)).

For security reasons, the equipment had a maximum urethral pressure level of 200 cm H_2O, which could have limited the reliability of measurements around this level. It furthermore prevented us from using measurements in the erect position where a pressure above 200 cm H_2O cm is often needed to open the urethra in continent women. Nonetheless, erect measurements might have been more appropriate when analyzing the urethral closure function.

We measured the urethral P_o during intra-abdominal pressure increase by straining well aware that leakage often occurs during faster pressure increases such as coughs. However, the urethral closure mechanism is very complex and the UPR technique does not allow reliable measurement during such a complicated dynamic event as a cough.

The cross-sectional study design of study III, the small number of women included and the SUI-severity of the patients may have limited the study. The results of correlations between $P_{o\text{-}rest}$ and APIR, respectively, and age and number of deliveries, respectively, should be regarded with caution as the data from SUI and continent women were pooled.

CONCLUSIONS

- The new ("fast") continuous technique for performing UPR while resting, squeezing and straining is described. The P_o is the same while the reproducibility of the parameters seems to be better compared with the traditional technique
- The novel parameters enabled characterization of the urethral closure function in terms of the permanent closure forces primarily generated by the sphincteric unit (measured by the $P_{o\text{-}rest}$), and the adjunctive closure forces primarily generated by the support system (measured by the APIR)
- The Urethral Closure Equation (UCE) which combines $P_{o\text{-}rest}$ <u>and</u> APIR provided a more detailed description of the efficiency of the closure function and the extent and nature of possible dysfunctions in the individual woman
- Expressing the combined effect of the permanent and adjunctive closure forces at 50 cm H_2O abdominal pressure, the $P_{o\text{-}Abd\ 50}$ revealed significant deficiencies in SUI women already at this relatively low abdominal pressure level
- The correlation of SUI with deterioration of the mid-urethral parameters confirms the importance of the mid-urethra area as the continence zone
- The UCE, $P_{o\text{-}Abd\ 50}$ and $P_{o\text{-}Abd\ 100}$, respectively, separated SUI and continent women and showed highly significant negative correlation with ICIQ-SF, pad test and number of incontinence episodes per week. Consequently, they can be used as SUI diagnostic tests and severity measures
- The $P_{o\text{-}rest}$ was unchanged after TVT, whereas the resting opening elastance increased 18%. Accordingly, at the resting state the TVT somewhat improves the closure function by increasing the resistance against the dilation of the urethra, which probably explains the decreased maximum urine flow rate after TVT
- The APIR increased in all patients after TVT, which indicates that the adjunctive closure forces were increased while the

permanent closure forces were virtually unchanged, regardless of the pre-operative dysfunction
- $P_{o\text{-}Abd\ 50}$, $P_{o\text{-}Abd\ 100}$ and the UCE demonstrated a more efficient urethral closure function and decreased SUI severity in all patients after TVT. Therefore they may be used as outcome measures after treatment

PERSPECTIVES AND FUTURE RESEARCH

PERSPECTIVES
- The new ("fast") UPR technique enables characterization of the individual urethral closure dysfunction based on deterioration of $P_{o\text{-}rest}$, APIR, or both
- This characterization may allow individual tailored treatment and thereby lead to improved outcome
- $P_{o\text{-}Abd\ 50}$, which combines the permanent and the adjunctive closure forces, has shown to be a simple and very efficient parameter to distinguish between continence and SUI

FUTURE RESEARCH:
The following issues remain to be further clarified:
- Change in $P_{o\text{-}rest}$, APIR, $P_{o\text{-}Abd\ 50}$ and UCE induced by pelvic floor muscle training and other conservative and surgical anti-incontinence treatments
- Change in $P_{o\text{-}rest}$, APIR, $P_{o\text{-}Abd\ 50}$ and UCE caused by pregnancy and childbirth, both vaginal and caesarian section
- Change in $P_{o\text{-}rest}$, APIR, $P_{o\text{-}Abd\ 50}$ and UCE by the course of time
- The origin of the urethral pressure while resting and during increased intra-abdominal pressure by combining UPR measurement with imaging
- UPR measurements during coughing
- Simultaneous UPR and cystometry

SUMMARY

Stress urinary incontinence (SUI) occurs when the bladder pressure exceeds the urethral pressure in connection with physical effort or exertion or when sneezing or coughing and depends both on the strength of the urethral closure function and the abdominal pressure to which it is subjected. The urethral closure function in continent women and the dysfunction causing SUI are not known in details. The currently accepted view is based on the concept of a sphincteric unit and a support system. Our incomplete knowledge relates to the complexity of the closure apparatus and to inadequate assessment methods which so far have not provided robust urodynamic diagnostic tools, severity measures, or parameters to assess outcome after intervention.

Urethral Pressure Reflectometry (UPR) is a novel method that measures the urethral pressure and cross-sectional area (by use of sound waves) simultaneously. The technique involves insertion of only a small, light and flexible polyurethane bag in the urethra and therefore avoids the common artifacts encountered with conventional methods. The UPR parameters can be obtained at a specific site of the urethra, e.g. the high pressure zone, and during various circumstances, i.e. resting and squeezing.
During the study period, we advanced the UPR technique to enable faster measurement (within 7 seconds by the continuous technique) which allowed assessment during increased intra-abdominal pressure induced by physical straining.

We investigated the urethral closure function in continent and SUI women during resting and straining by the "fast" UPR technique. Thereby new promising urethral parameters were provided that allowed characterization of the closure function based on the permanent closure forces (primarily generated by the sphincteric unit, measured by the $P_{o\text{-}rest}$) and the adjunctive closure forces (primarily generated by the support system, measured by the Abdominal to urethral Pressure Impact Ratio (APIR)). The new parameters enabled a more detailed description of the efficiency of the closure function and the extent and nature of a possible dysfunction in the individual woman.

The Urethral Closure Equation (UCE) and urethral opening pressure at an abdominal pressure of 50 cm H_2O ($P_{o\text{-}Abd\ 50}$), respectively, which combine the permanent and the adjunctive closure forces, could separate continent and SUI women and thus appear to be excellent diagnostic tests. Moreover the parameters showed highly significant negative correlation with ICIQ-SF, pad test and the number of incontinence episodes per week and are therefore valid as urodynamic severity measures.
UPR in SUI women before and after TVT demonstrated a more efficient urethral closure function after the operation. The $P_{o\text{-}rest}$ was unchanged suggesting that the sphincteric unit was virtually unaltered and hence the permanent closure forces unchanged. However, the resting opening elastance increased by 18% indicating that at the resting state the TVT somewhat improves the closure function by providing increased resistance against the dilation of the urethra, which probably explains the decreased maximum urine flow rate found after TVT in this and previous studies.
The APIR increased in all patients after TVT suggesting that the support system was re-established and thus the adjunctive closure forces improved, regardless of the type of pre-operative dysfunction. The new UPR parameters may be used as outcome measures after treatment.

REFERENCES

(1) Hunskaar S, Lose G, Sykes D, Voss S. The prevalence of urinary incontinence in women in four European countries. BJU Int 2004 Feb;93(3):324-30.

(2) Griffiths D, Kondo A, Bauer S, Diamant., Liao L, Lose G, et al. Dynamic testing. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. 3 ed. Plymouth, United Kingdom: Health Publications; 2005. p. 585-675.

(3) Chapple CR, Wein AJ, Artibani W, Brubaker L, Haab F, Heesakkers JP, et al. A critical review of diagnostic criteria for evaluating patients with symptomatic stress urinary incontinence. BJU Int 2005 Feb;95(3):327-34.

(4) Lose G. Simultaneous recording of pressure and cross-sectional area in the female urethra: A study of urethral closure function in healthy and stress incontinent women. Neurourol Urodyn 1992;11(2):55.

(5) Koelbl H, Nitti V, Baessler K, Salvatore S, Sultan A, Yamaguchi O. Pathophysiology of urinary incontinence, fecal incontinence and pelvic organ prolapse. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence. 4 ed. 2009. p. 255-330.

(6) Ghoniem G, Stanford E, Kenton K, Achtari C, Goldberg R, Mascarenhas T, et al. Evaluation and outcome measures in the treatment of female urinary stress incontinence: International Urogynecological Association (IUGA) guidelines for research and clinical practice. Int Urogynecol J Pelvic Floor Dysfunct 2008 Jan;19(1):5-33.

(7) Ashton-Miller JA, DeLancey JO. Functional anatomy of the female pelvic floor. Ann N Y Acad Sci 2007 Apr;1101:266-96.

(8) Hosker G, Rosier P, Gajewski J, Sand P. Dynamic testing. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence. 4 ed. 2009. p. 413-522.

(9) Schafer W. Some biomechanical aspects of continence function. Scand J Urol Nephrol Suppl 2001;35(207):44-60.

(10) Weber AM. Is urethral pressure profilometry a useful diagnostic test for stress urinary incontinence? Obstet Gynecol Surv 2001 Nov;56(11):720-35.

(11) Weber AM. Leak point pressure measurement and stress urinary incontinence. Curr Womens Health Rep 2001 Aug;1(1):45-52.

(12) Klarskov N, Lose G. Urethral pressure reflectometry; a novel technique for simultaneous recording of pressure and cross-sectional area in the female urethra. Neurourol Urodyn 2007;26(2):254-61.

(13) Griffiths D. The pressure within a collapsed tube, with special reference to urethral pressure. Phys Med Biol 1985 Sep;30(9):951-63.

(14) Klarskov N, Lose G. Urethral pressure reflectometry and pressure profilometry in healthy volunteers and stress urinary incontinent women. Neurourol Urodyn 2008;27(8):807-12.

(15) Klarskov N, Lose G. Urethral pressure reflectometry vs urethral pressure profilometry in women: a comparative study of reproducibility and accuracy. BJU Int 2007 Aug;100(2):351-6.

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

(17) Kim KJ, Ashton-Miller JA, Strohbehn K, DeLancey JO, Schultz AB. The vesico-urethral pressuregram analysis of urethral function under stress. J Biomech 1997 Jan;30(1):19-25.

(18) Ashton-Miller JA, Howard D, DeLancey JO. The functional anatomy of the female pelvic floor and stress continence control system. Scand J Urol Nephrol Suppl 2001;(207):1-7.

(19) Zacharin RF. THE SUSPENSORY MECHANISM OF THE FEMALE URETHRA. J Anat 1963 Jul;97:423-7.

(20) Pirpiris A, Shek KL, Dietz HP. Urethral mobility and urinary incontinence. Ultrasound Obstet Gynecol 2010 Oct;36(4):507-11.

(21) Rinne KM, Kainulainen S, Aukee S, Heinonen S, Nilsson CG. Dynamic magnetic resonance imaging of the behavior of the mid-urethra in healthy and stress incontinent women. Acta Obstet Gynecol Scand 2010 Mar;89(3):373-9.

(22) Bump RC, Copeland WE, Jr., Hurt WG, Fantl JA. Dynamic urethral pressure/profilometry pressure transmission ratio determinations in stress-incontinent and stress-continent subjects. Am J Obstet Gynecol 1988 Sep;159(3):749-55.

(23) Summitt RL, Jr., Sipes DR, Bent AE, Ostergard DR. Evaluation of pressure transmission ratios in women with genuine stress incontinence and low urethral pressure: a comparative study. Obstet Gynecol 1994 Jun;83(6):984-8.

(24) Dietz HP, Clarke B, Herbison P. Bladder neck mobility and urethral closure pressure as predictors of genuine stress incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2002;13(5):289-93.

(25) Schafer W. Biomechanical critique of current anatomical and functional concepts of urethral sphincter function. Neurourol Urodyn 1989;8:868-9.

(26) Fawcett T. An introduction to ROC analysis. Pattern Recognition Letters 2006;27:861-74.

(27) Trowbridge ER, Wei JT, Fenner DE, Ashton-Miller JA, DeLancey JO. Effects of aging on lower urinary tract and pelvic floor function in nulliparous women. Obstet Gynecol 2007 Mar;109(3):715-20.

(28) DeLancey JO. Why do women have stress urinary incontinence? Neurourol Urodyn 2010;29 Suppl 1:S13-S17.

(29) Shek KL, Pirpiris A, Dietz HP. Does levator avulsion increase urethral mobility? Eur J Obstet Gynecol Reprod Biol 2010 Dec;153(2):215-9.

(30) Viereck V, Nebel M, Bader W, Harms L, Lange R, Hilgers R, et al. Role of bladder neck mobility and urethral closure pressure in predicting outcome of tension-free vaginal tape (TVT) procedure. Ultrasound Obstet Gynecol 2006 Aug;28(2):214-20.

(31) Mutone N, Mastropietro M, Brizendine E, Hale D. Effect of tension-free vaginal tape procedure on urodynamic continence indices. Obstet Gynecol 2001 Oct;98(4):638-45.

(32) Martan A, Masata J, Svabik K, Drahoradova P, Pavlikova M, Hlasenska J. [Changes in values of urethral closure pressure and its position after TVT operation--predictive value of MUCP and VLPP for successful rate of this operation]. Ceska Gynekol 2005 Sep;70(5):370-6.

(33) Lo TS, Wang AC, Horng SG, Liang CC, Soong YK. Ultrasonographic and urodynamic evaluation after

tension free vagina tape procedure (TVT). Acta Obstet Gynecol Scand 2001 Jan;80(1):65-70.

(34) Atherton MJ, Stanton SL. The tension-free vaginal tape reviewed: an evidence-based review from inception to current status. BJOG 2005 May;112(5):534-46.

(35) Sander P, Moller LM, Rudnicki PM, Lose G. Does the tension-free vaginal tape procedure affect the voiding phase? Pressure-flow studies before and 1 year after surgery. BJU Int 2002 May;89(7):694-8.

(36) Lukacz ES, Luber KM, Nager CW. The effects of the tension-free vaginal tape on voiding function: a prospective evaluation. International Urogynecology Journal 2004;15(1):32-8.

(37) Yildirim A, Basok EK, Gulpinar T, Gurbuz C, Zemheri E, Tokuc R. Tissue reactions of 5 sling materials and tissue material detachment strength of 4 synthetic mesh materials in a rabbit model. J Urol 2005 Nov;174(5):2037-40.

(38) Falconer C, Soderberg M, Blomgren B, Ulmsten U. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. Int Urogynecol J Pelvic Floor Dysfunct 2001;12 Suppl 2:S19-S23.

(39) Sarlos D, Kuronen M, Schaer GN. How does tension-free vaginal tape correct stress incontinence? investigation by perineal ultrasound. Int Urogynecol J Pelvic Floor Dysfunct 2003 Dec;14(6):395-8.

(40) Dietz HP, Wilson PD, Gillies, Vancaillie. How does the TVT achieve continence? Neurourol Urodyn. 19, 393-394. 2000.

(41) Atherton MJ, Stanton SL. A comparison of bladder neck movement and elevation after tension-free vaginal tape and colposuspension. BJOG 2000 Nov;107(11):1366-70.

(42) Fritel X, Zabak K, Pigne A, Demaria F, Benifla JL. Predictive value of urethral mobility before suburethral tape procedure for urinary stress incontinence in women. J Urol 2002 Dec;168(6):2472-5.

(43) Rinne K, Kainulainen S, Aukee S, Heinonen S, Nilsson CG. Dynamic MRI confirms support of the mid-urethra by TVT and TVT-O surgery for stress incontinence. Acta Obstet Gynecol Scand 2011 Jun;90(6):629-35.

(44) Masata J, Martan A, Svabik K, Drahoradova P, Pavlikova M. Ultrasound imaging of the lower urinary tract after successful tension-free vaginal tape (TVT) procedure. Ultrasound Obstet Gynecol 2006 Aug;28(2):221-8.

(45) Koelle D, Windisch J, Doerfler D, Marth C, Kropshofer S. Effect of tension-free vaginal tape operation on urethral closure function. Urology 2006 Mar;67(3):524-8.

(46) Wang AC. An assessment of the early surgical outcome and urodynamic effects of the tension-free vaginal tape (TVT). Int Urogynecol J Pelvic Floor Dysfunct 2000;11(5):282-4.