Evolution\textsuperscript{Q1} of Midurethral and Other Mesh Slings – A Critical Analysis

Peter Petros\textsuperscript{1,2*} and John Papadimitriou\textsuperscript{3}

\textsuperscript{1}Academic Dept of Urology, Case Western University, Cleveland, Ohio
\textsuperscript{2}UNSW St Vincent’s Clinical School, Sydney, NSW, Australia
\textsuperscript{3}Department of Pathology and Laboratory Medicine, University of Western Australia, Perth, Western Australia, Australia

We analyzed our original experimental studies on which the midurethral sling was based with reference to FDA mesh warnings. We concluded that

1. Vascular/organ damage could be avoided by first penetrating the urogenital diaphragm.
2. A non-stretch tape minimizes obstruction and urethral damage.
3. A non-obstructive musculoelastic mechanism closes the urethra.
4. The strength of neocollagen (\textgreater 92.8 lbs/sq inch) indicates that little mesh is required for prolapse repair.
5. Foreign body (mesh) reaction is different from infection and is related to volume implanted
6. Urgency is potentially curable by repairing the suspensory ligaments
7. “Minislings” are promising for incontinence and POP, but more development is required.


Key words: integral theory; musculoelastic closure; pubourethral ligament; ureterovesical junction; urinary stress incontinence

INTRODUCTION

Recently, the FDA issued a warning on the use of mesh usage in pelvic organ prolapse (POP).\textsuperscript{3} Though midurethral sling surgery was largely exonerated, the warning nevertheless stimulated us to review our early experimental studies, as these have been used as an intellectual cornerstone to justify the use of mesh in prolapse surgery, wrongly so, as our work was based on strengthening ligaments, not creating stiff vaginal tissue, which needs to be elastic at all times. We found that our early works shed considerable light not only on the many issues giving rise to the FDA warnings, for example, tape erosion, infection, obstructed urination, organ, and vascular damage, but also on many clinical controversies, surgical cure of “mixed” incontinence, urgency, pelvic pain, and “obstructed” micturition.

1986—Origins of the Midurethral Sling and Integral Theory

In 1986, the dominant theory for USI pathogenesis was the “Pressure Equalization” theory.\textsuperscript{2} The main operations were the Kelly repair, Burch colposuspension, fascial bladder neck sling, major painful operations, associated with urinary retention.

The midurethral sling\textsuperscript{3} and Integral Theory\textsuperscript{4} originated from an observation of dense fibrous tissue around a Teflon tape used in the Cato colposuspension.\textsuperscript{5} We reasoned that implanting a tape for 6 weeks and then removing it, would reinforce the pubourethral ligament (PUL) sufficiently to cure USI. Two prototype midurethral sling operations were performed at RPH in 1986. Both patients were discharged next day, cured of USI, with minimal pain and no urinary retention.

1987—Animal studies were performed in 1987.\textsuperscript{6} Our aim was to use the collagenous foreign body reaction of an implanted Mersilene tape in a positive way, to reinforce the damaged PUL. A tunneller with a 90° curve (Fig. 1) allowed close application to the pubic bone, minimizing bladder perforations.

Thirteen large dogs had a non-stretch Mersilene tape implanted as an inverted “U,” both ends free in the vagina for up to 19 weeks. They remained afebrile and well, though 10/13 developed a (sterile) suprapubic purulent sinus. Histology: foreign body inflammatory reaction (FBIR) with multinucleated giant cells, rather than infection; Radioactive Gallium studies: minimal inflammation around tapes. A collagenous tunnel formed around the Mersilene tape, allowing easy removal postoperatively. Indian ink injected around tapes before removal identified the channel after the dogs were sacrificed. Sinuses closed within 3 days of tape removal. The artificial collagenous “neoligament” was 0.2–2 cm in width (Fig. 2).

The “neoligament” was invariably attached by thick fibrous tissue to pubic bone, vagina, muscle, and skin (Fig. 2). In situ

Additional supporting information may be found in the online version of this article.

Abbreviations: DI, Urodynamic detrusor instability; FDA, Food and Drug Administration; FBIR, foreign body inflammatory reaction; POP, pelvic organ prolapse; RPH, Royal Perth Hospital, Perth Western Australia; TVT, tension-free vaginal tape; TOT, transobturator tape; TFS, tissue fixation system; UI, urge incontinence; USI, urinary stress incontinence.

Conflict of Interest: Peter Petros is the co-inventor of the midurethral sling (TVT 1995) the posterior sling “Infracoccygeal Sacropexy” 1997) and the TFS tensioned sling (2005). John Papadimitriou author has no conflict of interest.

Peter Petros and John Papadimitriou contributed to the conceptualization and writing of the manuscript.

*Correspondence to: Peter Petros, DSc, PhD, D5, MB, BS, MD, FRCOG, FRANZCOG, CU, Academic Dept of Urology, Case Western University, Cleveland, OH.
E-mail: pp@kvinno.com
Received 3 July 2012; Accepted 9 August 2012
Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/nau.22308

© 2012 Wiley Periodicals, Inc.
tapes were initially surrounded by granulation tissue: macrophages, granulocytes, lymphocytes, and multinucleated giant cells and a thick outer layer of vascularized collagenous connective tissue, expected characteristics of an FBIR; initial collagen III (argyrophilic), maximal at 4 weeks, was subsequently replaced by collagen I (argyrophobic). Histologic examination 6 weeks after tape removal demonstrated a collagenous tunnel forming an artificial "neoligament" (Fig. 2), with only little granulation tissue. Macrophages infiltrated the interstices in all Mersilene tape specimens. A collagenous "neoligament" formed in the aftermath of the inflammatory reaction is immensely strong: one specimen tore out of a tensiometer's grips at 0.64 megaPascals, (92.8 lbs/sq inch). 7

Lessons Learnt from the Animal Studies

1. Tape implantation even with sinus formation was safe: cutaneous sinuses resulted from FBIR, not infection. FBIR is characterized clinically by an afebrile state, histologically by giant cells and sometimes, sterile pus, which like a splinter, may distend the tissues to cause pain. FBIRs are clinically benign, and quite different to those of infection, which are not.

2. Bacterial growth, where present, was "mixed" nature, with low counts. Infective inflammation was uncommon, generally caused by an infected hematoma with pyrexia, and isolation of pathogenic bacteria.

3. Three dogs had no sinuses indicating individual immunological variation in tissue reaction.

4. Macrophages were found in the interstices of Mersilene tapes, indicating that whatever the cause of the sinuses, it was not absence of macrophages in the spaces.

5. The collagenous neoligament is enormously strong, indicating that large meshes are not required to support a 100 g uterus, or an even smaller vagina.

6. The inflammatory reaction from the tape glued it to anything it touched, "tissue welding."

On the positive side: Small strips of tensioned tapes applied transversely cure POP 9,10 reinforcing ligaments and linking together perineal bodies and levator hiatus structures, to prevent lateral displacement and POP during straining.

On the negative side: Excess FBIR from large meshes may damage organs and "glue" vagina to rectum to cause dyspareunia, fistulae, and other complications, as per the FDA warning.

1988 2nd group of 30 prototype midurethral sling operations were performed in 1988. 2 An adjustable Mersilene sling (Fig. 3) was inserted immediately behind pubic bone. Postoperatively the sling was lowered sufficiently to allow normal micturition and was removed after 6 weeks. Obstructed
micturition and urgency improved as the sling was lowered. All 30 patients were continent with a normal stream.

**Pre-operative X-ray studies** indicated that a tape inserted immediately behind the pubic symphysis became sited at the midurethra (Fig. 4). Eight patients with a starting position of bladder neck at or below the lower border of pubic symphysis were cured without elevation, invalidating Enhorning’s “Pressure Transmission Theory.” When the tape was grasped with a hemostat, and the patient strained, three directional forces acting against the midurethra became evident on X-ray (Fig. 4), suggesting the presence of a bidirectional musculoelastic closure mechanism acting against the PUL.

**Lessons Learnt from the “Lowering” of the Tape Experiment**

1. Excessive tightness may cause obstruction and urgency.
2. A tape can cure USI without obstruction or retention.
3. Bladder neck elevation is not required for USI cure: a musculoelastic mechanism acting against a competent PUL effected urethral closure.¹¹

**The musculoelastic hypothesis**, Figures 5 and 6, Video 1, was substantially validated in 1999:¹¹ a hemostat inserted unilaterally immediately behind the pubic symphysis (“Simulated operation”) restored normal geometry and continence (arrow, Fig. 5). Urodynamically, distal, and proximal urethral pressure rise were observed during this manoeuvre.¹²

**“Mixed incontinence”** Of 30 USI patients, 25 also had urge incontinence (UI) and they reported cure of both symptoms post-operatively.³ When the tape was removed, 50% reported recurrence of both USI and UI. Subsequently, bilateral leaf shaped incisions improved both stress and urge symptoms in some failed cases. These results, subsequently validated by Rezapour and Ulmsten,¹³ suggested a common etiology for USI and urgency based on connective tissue laxity.

**1990–1993 The 3rd group of prototype operations** were performed under local anesthetic/sedation, using a lightweight instrument with a delta wing for more precise orientation of the tip and a Mersilene tape.¹⁴ This method eventually led to the intravaginal slingplasty,¹⁵–¹⁷ better known as the “TVT” (Fig. 7).

A hole was made through the urogenital diaphragm immediately behind the pubic bone, and the applicator inserted under direct vision, with the delta wing indicating the position of the tip. With the patient coughing, the tape was raised in a staged manner until continence was achieved. There were few instances of post-operative urinary retention.
post-operative pain was minimal and patients were able to return to normal duties within days. We found that Mersilene tape had an unacceptably high erosion rate. Though this was essentially harmless, the discharge was often offensive and distressing to the patients.

Subsequently, the use of a polypropylene tape largely solved the erosion problems encountered with Mersilene. In 1992, this “tension-free vaginal tape” principle was applied for repair of uterine/apical prolapse using the infracoccygeal sacropexy operation. In such patients, a high rate of cure was observed in patients with symptoms of nocturia, urgency, and some types of pelvic pain.

1. USI and “mixed” incontinence were surgically curable by placing small lengths of tape at midurethra.
2. A hole in the urogenital diaphragm preceding insertion of the instrument gave greater control of the instrument.
3. The staged technique for tightening the tape was accurate and effective.
4. Only a permanent tape gave good longer-term results for USI surgery.
5. Polypropylene is the best material for implantation.
6. The “tension-free vaginal tape” principle, using short lengths of tape gave good results for uterine/apical prolapse repair using the infracoccygeal sacropexy (posterior sling). Large sheets of mesh were not required. This operation gave a high cure rate for nocturia, urgency, and some types of pelvic pain.
7. Heavy densely knit tapes (such as Mersilene, polypropylene Amid type 3) are more likely to cause excessive tissue fluid reaction, surfacing, and erosion. The higher the density of the implant, the more the erosion.

Questions arising on the nature of the unstable bladder (1990–1997) From the earliest to later urodynamically monitored studies the high rates of surgical cure for urge incontinence (UI), frequency, and nocturia provoked the question, “what is the mechanism for surgical cure of unstable bladder symptoms?”

1993 A urodynamically based study indicated that urodynamic “detrusor instability” (DI) was consistent with a prematurely activated micturition reflex, thus providing an anatomical basis for the hypothesis flowing from the Theory, that a lax vaginal membrane may have prematurely activated the micturition reflex, and that surgical cure of UI is possible by tightening the vaginal membrane.

1999 Low compliance was consistent with a partially activated, but controlled, micturition reflex, while the sinuous urodynamic pattern characteristic of instability was an expression of a struggle between two feedback loops, the micturition and closure reflexes. In a small number of cases, it was possible to reverse a urodynamic DI pattern by gentle digital pressure below bladder base. See Video 2.

Trampoline analogy The concept of bladder base stretch receptors “N” Figure 8 supported by a stretched vaginal membrane explains improvement in urge symptoms after midurethral or posterior sling surgery, and with Simulated Operations which also work by restoring the insertion point(s) of the pelvic muscles which stretch the vaginal membrane (arrows, Fig. 8). The presence of stretch receptors “N” can be verified in some patients by stretching the bladder base upwards to activate the micturition reflex (see Video 3).

Lessons learnt from examining the nature of urgency and urodynamic detrusor overactivity
1. In a non-neurogenic patient, urgency and urge incontinence are most likely clinical manifestations of a prematurely activated micturition reflex caused by inability of a lax vaginal membrane to support the bladder base stretch receptors; in turn, a consequence of lax suspensory ligaments inactivating the musculoelastic mechanism which stretches the vagina.
2. Urodynamic detrusor overactivity in the female is consistent with a secondary urodynamic manifestation of a prematurely activated micturition reflex, as it can, in some cases, be controlled or even reversed. See also Video 2.
3. In patients with such anatomic causes, urgency and urge incontinence are potentially curable surgically by repairing lax ligaments/vagina.

Desquamated decomposing vaginal cells attached to the tape created a smell of dead tissue. In the original group of 30 patients where the tape lay in the vagina for 6 weeks, discharge and odour were controlled by vinegar douches.

Neuourology and Urodynamics DOI 10.1002/nau
Evolution of Midurethral and Other Mesh Slings

A

Fig. 8. Trampoline analogy-function. How the muscle forces control peripheral neurological function. Like a trampoline, laxity in even one suspensory ligament, PUL (pubourethral), CL (cardinal), ATFP or USL (uterosacral), may prevent the muscle forces (arrows) from tensioning the vaginal membrane. The stretch receptors “N” cannot be supported, and fire off prematurely. The cortex perceives the afferent impulses as urge symptoms. Surgical restoration of PUL, USL, and CL explain urgency cure with a midurethral sling,12,16 cystocele repair, and posterior sling repair.16,29 See also Videos 2 and 3.

1995–2011 Commercialization The subsequent course of this new direction in surgery was driven by major international medical companies. Viewed with the wisdom of hindsight, commercialization had a bright side and a dark side.

The bright side of commercialization Gynecare initiated an extensive marketing campaign which spread the midurethral sling and the underlying Integral Theory worldwide, creating a revolution in the treatment of USI. Within a few short years the previous “gold standard,” the Burch Colposuspension was relegated to history. Tyco marketed the infracoccygeal sacropexy, or posterior IVS sling for apical/uterine prolapse. In addition to prolapse repair, cure of urgency, nocturia, abnormal and emptying was also reported.17

The dark side of commercialization Complications began to appear, those caused by instrument misuse and those caused by the tape. The exponential spread of the TVT technique made it impossible to adhere to the original strict training protocols. It became a free for all “See one, do one, teach one.” Not all errors were due to poor teaching, however.

The instrument, the surgeon and surgical methodology: Bladder perforation was an early problem, but always in the dome of the bladder, not unlike a suprapubic catheter. Injury to major blood vessels, nerves, small bowel, and large retropubic haematomas were a serious problem, with several fatalities. Though ascribed to “faulty technique,” the ultimate cause of these problems may have been removal of some core steps from the original operations—perforating the urogenital diaphragm prior to insertion of the applicator, preventing excessive thrust during insertion; a non-elastic (Mersilene) tape; control of bleeding from a subpubic sinus perforation by digital pressure.

The commercial instrument introduced two sharp trochars, eliminating the necessity for a pre-insertion hole, which masked bleeding from the venous sinuses below pubic bone, which may collect in the Space of Retzius and proceed unhindered cephalad. The heavy screw-on handle removed the operative sensitivity of a light instrument, so the instrument was often pushed forcibly at 45° before being directed upwards. Prior perforation not only gives greater control, it reveals potential bleeding which can be addressed with digital pressure.

The Tape

Only two polypropylene (PP) tapes were commercially available in early 1990s, both flawed: an elastic Amid type 1 “monofilament” with wide spaces (Gynecare) which narrowed to thin cord on stretching; a heavier non-stretch Amid type 3, composed of multiple grouped fibers, 20–30 μm in diameter, with narrow 75–200 μm spaces (Tyco). Amid’s20 was incorrect in his statements that a macrophage required a 75 μm space to be functionally efficient. Macrophages were demonstrated in 5 μm spaces21 or by developing lamellodemia, traversing interendothelial gaps 1 μm in width.22 Nevertheless, Amid’s classification is important as a reference point for physical characteristics of implanted materials.

Elastic Type 1 tape stretches when pulled upwards. Initially, the elastic tape was applied directly onto the wall of the urethra. Restoration of elasticity in the subsequent 24 h may have been responsible for many post-operative incidents of urinary constriction, retention, and even urethral perforation and fistula. Placed under stretch the diamond-shaped tapes stretch like a steel wire, sometimes transecting the urethra to cause fistula. A space left between tape and urethra has helped this problem, but this method remains imprecise; too tight-retention; too loose-incontinence. The question is “How much space to leave.” Clearly more tape insertion and more elastic restoration occurs in a 120 kg woman than in a 45 kg woman.

Non-elastic Type 3 “multifilament” tape: Was the only truly non-stretch PP tape available in the mid 1990s to mid 2000s. Applied to the wall of urethra, there was no post-operative retraction, and few retentions. Nevertheless, the higher concentration of polypropylene per unit volume had the potential to provoke larger FBIRs around the tapes with greater likelihood of slippage, surfacing and erosions24 or even pain.24 Though the histology (granulomas), the clinical characteristics of the reaction and the time frame (24 months duration) were indicative of a FBIR, many such cases were described as “infection.” We emphasize the importance of understanding the difference between foreign body induced inflammation (benign) and infection (not benign), especially in the context of the FDA warnings on mesh implantation and consequent medio-legal suits. Though entrapped pus from a foreign body reaction may cause pain,24 it is sterile, and like a splinter, symptoms settle immediately on tape removal; infected pus contains heavy concentrations of pathogenic bacterial species. Infection is potentially serious.

Note Pus is only the liquefactive necrosis of granulocytes and the tissue in which they have invaded – bacteria are not necessarily involved.

2000–2010—Application of the surgical tape principle to other operations

The transobturator “TOT” midurethral sling (Delorme)25 in 2001 was a significant advance, with equivalent results for USL, with fewer complications, though possibly less effective in ISD (Intrinsic sphincter defect) patients. The infracoccygeal sacropexy (posterior sling)17 was first performed in 1992 under LA/sedation in a woman with emphysema, uterine prolapse, and symptoms comprising the “posterior fornix syndrome” (urgency, nocturia, pelvic pain, and abnormal...
emptying). However, the infracoccygeal sacropexy did not repair the anterior vaginal wall, which prolapsed subsequently in 16–20% of patients. Many commercial companies attached large mesh sheets to TOT tapes for cystocele repair and to the infracoccygeal sacropexy tapes for rectocele repair, combining both for uterine/apical prolapse repair. These blocked but did not correct the herniation (Dietz, personal communication), often causing pain and other complications, resulting in FDA warnings.

**2005 Minislings** are a promising new direction, as they utilize only small tape strips, potentially avoiding problems inherent in the FDA warnings.

*Use in urinary stress incontinence:* Unlike the TVT and TOT which have long lengths of tape, “minislings” rely on the anchor “grip” to resist restorative forces from tissues they compress. Anchor grip varies with different “kits” as do results reported. In general, achieving the correct tension is difficult with untensioned minislings, as insertion and tightening are done simultaneously. They compress the periurethral tissue and so are subject to restorative tissue elastic forces post-operatively which tend to loosen the tape. Tensioned minislings (Fig. 9) work on a different principle. Soft-tissue anchors with high pullout strength are inserted and the tape is tightened as a separate movement. Though 5 year RCT data and high cure rates for ISD using the TFS tensioned midurethral sling have been reported, more data is required.

*Use in pelvic organ prolapse (POP):* The same “Autogenic Neoligament” surgical principle used for the TVT has been applied for repair of POP since September 2003—small lengths of tape are used to reinforce the damaged ligaments causing organ prolapse. Applied in the position of uterosacral, cardinal, ATFP, and perineal bodies (Figs. 9–12) the tapes accurately reinforce these structures in the manner of ceiling joists to cure cystocele, uterine/apical prolapse, rectocele, and descending perineal syndrome, even anterior rectal wall intussusception and hemorrhoids and symptoms POP. Unlike large sheets of mesh, the transversely positioned tapes mimic normal structural anatomy. They largely avoid organ spaces,
do not create rigid vaginas and they preserve vaginal elasticity. Vaginal elasticity is critical for control of urgency symptoms. Though promising 3 year results have been presented, this technology is best regarded as being still in the evaluation phase.

Future Directions

Return to a non-stretch tape as we see it, brings with it an anatomical precision. Ideally, the tape should be lightweight monofilament, Amid type I. The tape needs to touch but not indent the urethra so as to predictably restore the musculoelastic mechanisms for continence without significant obstruction, as demonstrated.

Ageing population: Urinary and fecal incontinence are major indications for admission to Nursing Homes for at least 50% of patients. Early data from Japan applying TFS sling operations (Figs. 9–12) in aged patients often under Local Anesthesia suggest a muscleelastic mechanism activating closure. Neurourol Urodyn 2003;22:192–7.

Evolution of Midurethral and Other Mesh Slings

REFERENCES

8. Petros PE, Richardson PA. The midurethral TFS sling—A ‘micro’ method for cure of stress incontinence—preliminary report,