

# URINARY INCONTINENCE

- **Surgery for stress incontinence**
- **A pain drug for OAB?**
- **Does genetics affect risk?**

**A**nother year is drawing to a close and, looking back, what have we learned about urinary incontinence? A clear understanding of etiology stubbornly eludes us. How would a clear understanding of etiology affect management? It's difficult to be specific until we actually do understand it, but generally:

- **We could gear diagnosis** toward identifying a particular abnormality, rather than the current state of making a purely descriptive diagnosis.
- **We could target treatment** to the particular abnormality (or abnormalities) in the individual patient.
- **We could target prevention** to subgroups at high risk for developing incontinence. Prevention could consist of strategies to avoid or mitigate the effects of environmental exposures or life events, to prevent the accumulation of a critical number of "hits," or to increase a woman's tolerance or threshold at which incontinence would otherwise occur.

## The "multiple-hit" theory probably applies to urinary incontinence, too

The "multiple-hit" theory usually ascribed to cancer probably also fits the development of urinary incontinence, a likewise multifaceted condition. A woman begins life with genetic predisposition at some

level that we cannot currently measure, but which is influenced by the environment (eg, nutrition, toxic exposures) and life events (eg, childbirth, aging)—all of which determine her likelihood of developing incontinence.

Until the time when we do have a clear understanding on which to base diagnosis, treatment, and prevention, of course, we must continue to manage incontinence with the tools of today.

A few pieces of the puzzle are slowly coming together.

## What's new

### How are slings holding up to further scrutiny?

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2 large studies of twins [Page 51](#)



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**TABLE 1**

**Comparison of selected multifilament and small-pore mesh products**

REFERENCE	SLING PRODUCT	EROSION RATE	MANAGEMENT
Abdel-Fattah et al (2006)	Obtape	7.3% (14 of 192)	7: partial excision 7: complete excision with infection
	TVT-O	1.8% (2 of 112)	1: partial excision 1: vaginal closure
Yamada et al (2006)	Obtape	13.4% (9 of 67)	9: complete excision (1 with abscess)
	Monarc	0 of 56	—
Siegel et al (2005)	IVS	17% (6 of 35)	6: complete excision (1 with pelvic abscess)

## Surgery for stress incontinence

**E**ven as new surgical techniques or modifications continue to proliferate, evidence to guide clinical practice accumulates belatedly. MEDLINE lists 325 articles since 1996 (combining surgical mesh and urinary incontinence, limited to human females and published in English). Nonetheless, a consensus may be emerging that the safest synthetic material is monofilament polypropylene with pore size larger than 70 µm.

Unfortunately, by the time research reports are published showing higher complications with certain products, countless women have already been treated.

Mesh erosion (or exposure, extrusion), sometimes accompanied by infection, is a common complication when multifilament or small-pore meshes are used. Even worse, companies commonly withdraw products, modify them, and re-introduce them to the market, accompanied by intensive marketing but, as with the original product, without any real evidence of safety and effectiveness.

In an ideal world, clinicians (and patients) would insist on evidence before accepting new products and techniques. Failing that, clinicians (and patients!) should clearly understand that all new products and techniques are experimental until they are proven equal to or bet-

ter than traditional techniques. As we have learned with the most subtle differences between synthetic materials, “almost the same” or “looks the same” is not the same.

Among the most important evidence on slings this year are reports of investigations that demonstrated what should *not* be done.

### Are monofilament, large-pore mesh products safer?

Abdel-Fattah M, Sivanesan K, Ramsay I, Pringle S, Bjornsson S. How common are tape erosions? A comparison of two versions of the transobturator tension-free vaginal tape procedure. *BJU Int.* 2006;98:594–598.

Yamada BS, Govier FE, Stefanovic KB, Kobashi KC. High rate of vaginal erosions associated with the Mentor Obtape. *J Urol.* 2006;176:651–654.

Siegel AL, Kim M, Goldstein M, Levey S, Ilbeigi P. High incidence of vaginal mesh extrusion using the Intravaginal Slingplasty sling. *J Urol.* 2005;174:1308–1311.

**T**he risk of vaginal erosion is much higher with synthetic meshes used for sling procedures when the mesh is multifilament and/or small-pore (<70 µm). In some cases, companies have replaced products (Mentor Obtape small-pore polypropylene sling product was replaced with macroporous Aris), whereas others continue to market

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**A consensus may be emerging that the safest synthetic material is monofilament polypropylene with pore size larger than 70 µm**

products reported to have unacceptably high rates of vaginal erosion and mesh extrusion (Intravaginal Slingplasty multifilament mesh) (TABLE 1).

## Avoid cadaveric fascia in sling procedures

Howden NS, Zyczynski HM, Moalli PA, Sagan ER, Meyn LA, Weber AM. Comparison of autologous rectus fascia and cadaveric fascia in pubovaginal sling continence outcomes. *Am J Obstet Gynecol.* 2006;194:1444-1449.

**E**vidence has accumulated that sling procedures performed with cadaveric fascia have substantially worse continence outcomes, compared with those using autologous fascia. In a retrospective cohort study of 150 women with cadaveric fascial slings and 153 women who had autologous rectus fascial slings, urinary incontinence (16 vs 5 per 100 women-years) and reoperation for stress incontinence (4 vs 1 per 100 women-years) occurred more frequently after cadaveric versus autologous rectus fascial slings.

## Should xenograft materials be used in sling procedures?

Giri SK, Hickey JP, Sil D, et al. Long-term results of pubovaginal sling surgery using acellular cross-linked porcine dermis in the treatment of urodynamic stress incontinence. *J Urol.* 2006; 175:1788-1792.

**S**everal companies market specific products integrated into sling techniques, such as In-First Ultra (porcine dermal matrix secured with bone anchors) and Stratasis (porcine small intestinal submucosa in urethral sling and tension-free versions). Other companies market only the xenograft for application in sling procedures, such as Pelvicol (acellular porcine collagen matrix). However, relatively little information is available to support or discourage use of xenograft materials in sling procedures.

Giri et al found worse outcomes using Pelvicol compared with autologous rectus

fascia for pubovaginal slings. With 3-year follow-up, 54% (26 of 48 women) with Pelvicol were considered successfully cured or improved, compared with 80.4% (37 of 46 women) with rectus fascia. Of interest, women continued to report recurrent incontinence with Pelvicol through the 3-year period, whereas women with rectus fascia had recurrence within the first 9 months after surgery.

## Midurethral slings: Retropubic or transobturator?

Waltregny D, Reul O, Mathantu B, Gaspar Y, Bonnet P, de Leval J. Inside out transobturator vaginal tape for the treatment of female stress urinary incontinence: interim results of a prospective study after a 1-year minimum followup. *J Urol.* 2006;175:2191-2195.

Morey AF, Medendorp AR, Noller MW, et al. Transobturator versus transabdominal midurethral slings: a multi-institutional comparison of obstructive voiding complications. *J Urol.* 2006;175:1014-1017.

**M**idurethral sling placement was modified from the retropubic to the obturator approach with the objective of reducing the risk of major bladder and urethral injury and vascular complications. Does the obturator approach actually have fewer intraoperative complications compared with the retropubic approach? Unknown. (As noted below, even within retropubic procedures, it is possible—although currently unknown—that vaginal and abdominal approaches have different complication rates.) This is a good news—bad news problem:

- The good news is that major injuries with any approach are relatively uncommon.
- The bad news is that a comparative trial would require a large sample size to determine a difference, even a clinically important difference, among the approaches.

Results of the obturator approach are beginning to appear in the literature as case series and uncontrolled comparative studies. Waltregny et al reported cure of stress incontinence in 91% of 99 patients after 1 year of follow-up. Morey et al reported

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**Xenograft slings have worse continence outcomes than autologous fascia**

**TABLE 2**

**Comparison of 2 retropubic midurethral slings**

OUTCOMES	GYNECARE TVT	SPARC	STATISTICAL SIGNIFICANCE
<b>Subjective continence</b> Series by Gandhi et al RCT by Lord et al	86% (61 of 71) 87% (128 of 147)	60% (28 of 47) 76% (117 of 153)	0.001 0.03
<b>Objective stress continence</b> Series by Gandhi et al RCT by Lord et al	95% (58 of 61) 97.3% (143 of 147)	70% (32 of 46) 97.4% (148 of 152)	<0.001 NS
<b>Follow-up</b> Series by Gandhi et al (median, range) RCT by Lord et al	17 weeks (6–197) 6 weeks	16 weeks (6–129) 6 weeks	— —
<b>Retention requiring reoperation</b> Series by Gandhi et al RCT by Lord et al	2.7% (2 of 73) 0 of 147	2.0% (1 of 49) 6.5% (10 of 154)	NS 0.002
<b>Mesh erosions*</b> RCT by Lord et al	4.8% (7 of 147)	10.5% (16 of 152)	0.08

\*Mesh erosions not reported in Gandhi et al.

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**NIH-sponsored study will compare obturator and abdominal approaches**

similar continence outcomes: 89% success for 154 patients after the obturator approach compared with 86% success for 350 patients after the abdominal approach, although follow-up in the abdominal group was substantially longer (mean 20 months, range 18–26) than in the obturator group (mean 9 months, range 6–16). Of interest, urethrolisis was performed more frequently in the abdominal group (2.3%) than in the obturator group (0%).

Randomized trials are necessary to obtain unbiased comparisons of techniques. Investigators in the NIH-sponsored Urinary Incontinence Treatment Network are currently performing a randomized trial comparing obturator and abdominal approaches with midurethral slings for women with stress and stress-predominant mixed incontinence. The primary outcome will compare objective and subjective treatment success between the 2 groups at 1 and 2 years after surgery. Enrollment is expected to be complete by early 2008, and 1-year follow-up by early 2009. Stay tuned for the results!

**Retropubic midurethral slings: Which brand?**

Gandhi S, Abramov Y, Kwon C, et al. TVT versus SPARC: comparison of outcomes for two midurethral tape procedures. *Int Urogynecol J Pelvic Floor Dysfunct.* 2006;17:125–130.

Lord HE, Taylor JD, Finn JC, et al. A randomized controlled equivalence trial of short-term complications and efficacy of tension-free vaginal tape and suprapubic urethral support sling for treating stress incontinence. *BJU Int.* 2006;98:367–376.

**A**s the first midurethral sling, the tension-free vaginal tape (Gynecare TVT) has the most evidence and longest follow-up available in the literature. It was originally described using the vaginal approach (“bottom-up”); the company now markets all 3 approaches: vaginal, abdominal (“top-down”), and obturator. Other companies market different products along the same lines, but it cannot be assumed that midurethral slings are interchangeable. Studies are starting to appear that compare different retropubic midurethral slings. In a retrospective case series (Gandhi et al) and a randomized trial (Lord et al), Gynecare TVT had better continence outcomes compared with SPARC (TABLE 2).

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## A pain drug for OAB?

**P**articularly for urge incontinence and associated symptoms falling under the heading of “overactive bladder,” new drugs are always being developed and existing drugs can be found to have a potentially new application. Drugs recently added to those FDA-approved for urge incontinence have relied primarily on their anticholinergic effects. In contrast, tramadol, a drug FDA-approved for pain relief (marketed in the United States as Ultram), was tested for this use. Although the mechanism of action is unknown, the authors proposed a possible change in dopamine receptor activation.

### Treated group improved, placebo group did not

Safarinejad MR, Hosseini SY. Safety and efficacy of tramadol in the treatment of idiopathic detrusor overactivity: a double-blind, placebo-controlled, randomized study. *Br J Clin Pharmacol*. 2006;61:456–463.

**T**his randomized, placebo-controlled trial included 76 men and women with detrusor overactivity. The study population was relatively young, with mean ages of 39 and 37 years in the drug and placebo groups, respectively, and included about 2/3 women. At a sustained-release dose of 100 mg twice a day for 12 weeks of

study, tramadol was effective for reducing the number of urge incontinence episodes per 24 hours from a baseline mean of  $3.2 \pm 3.3$  episodes to a mean of  $1.6 \pm 2.8$  episodes. In addition, frequency of voiding per 24 hours was reduced (baseline mean  $9.3 \pm 3.2$  episodes, to  $5.1 \pm 2.1$ ) and the mean volume per void increased substantially ( $158 \pm 32$  mL, to  $198 \pm 76$  mL) without an increase in postvoid residual urine volume.

In contrast to the results of many placebo-controlled drug trials and even with the use of 24-hour voiding diaries every 2 weeks for the 12-week study, the placebo group showed essentially no change in clinical and urodynamic outcomes. For example, the number of urge incontinence episodes per 24 hours was unchanged, from a baseline mean of  $3.3 \pm 3.1$  episodes, to a mean of  $3.1 \pm 3.0$  after 12 weeks. Nausea was the most commonly reported side effect (18% vs 5% in the drug and placebo groups, respectively); 2 of 35 participants in the tramadol group dropped out of the study due to nausea.

**Confirmation of these results** and further study may shed light on the complex control of normal voiding and the true etiology behind the symptoms that we call “detrusor overactivity,” and potentially open a new class of drugs for treatment.

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**Tramadol was effective for reducing the number of urge incontinence episodes**

## Delivery mode and genetic influences on urinary incontinence

Rohr G, Kragstrup J, Gaist D, Christensen K. Genetic and environmental influences on urinary incontinence: a Danish population-based twin study of middle-aged and elderly women. *Acta Obstet Gynecol Scand*. 2004;83:978–982.

Goldberg RP, Abramov Y, Botros S, et al. Delivery mode is a major environmental determinant of stress urinary incontinence: results of the Evanston–Northwestern Twin Sisters Study. *Am J Obstet Gynecol*. 2005;193:2149–2153.

**T**he genetic predisposition for urinary incontinence, seen in clinical practice as clustering in families—mothers, daughters, sisters—has been long suspected, and

has been supported in recent studies of nature’s gift to genetic research—twins. In a study of more than 1,000 Danish twins in 2 age groups, Rohr et al were able to quantitatively estimate the heritable component for urinary incontinence, which was categorized by questionnaire into urge, mixed, and stress incontinence. The study included 548 monozygotic twin pairs (who share identical genetic material) and 620 dizygotic twin pairs (who, on average, share 50%

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## UPDATE

URINARY INCONTINENCE CONTINUED

of their genes like ordinary sisters).

**Urge incontinence**, in both age groups, had a similar level of heritability: 42% for ages 46–68 and 49% for ages 70–94.

**Mixed incontinence** had a lower level of heritability: 27% in middle age and 55% in the older group.

**Stress incontinence** in the older group had a significant heritable component at 39%, but stress incontinence in the middle-aged group was more strongly associated with environmental factors than with heritability.

Another study focused on stress incontinence in a study of 271 monozygotic twin pairs with a mean age of 47 years. Within the 173 parous twin pairs, environmental factors associated with stress incontinence were identified: age, parity, obesity, and mode of delivery.

**Childbirth and genetic factors.** These data clarify an important area of (apparently) inconsistent epidemiologic literature on the role of childbirth, and particularly mode of delivery, in lifetime risk of urinary incontinence. The inconsistency resolves once age of the study cohort and type of incontinence are considered. Stress incontinence is influenced most strongly by mode of delivery in middle-aged women. Later in life, genetic factors play a more important role in risk of stress incontinence, and mode of delivery becomes less important. Urge incontinence, perhaps developing along a different etiologic path than stress incontinence, is strongly influenced by heritability in both middle-aged and older women; environmental factors influencing the development of urge incontinence are less important through the lifespan.

**Nonetheless, indications of a genetic component** do not begin to tell us what exactly is affected that increases the likelihood of urinary incontinence. Speculation is easy enough—perhaps the inherent strength, elasticity, or regeneration potential of critically important tissues in the urethra and pelvis is affected—but the details are not yet fully known.

Again, until we have a clearer understanding, we must continue to manage incontinence with the tools of today. ■

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