Trends-in-Medicine

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by Lynne Peterson

SUMMARY

Doctors are increasingly preferring transobturator slings to TVT slings. Mini-slings are seen as interesting but still very experimental. The prediction is that if they pan out, they will capture the market.

♦ Off-label use of Allergan's Botox to treat refractory urge incontinence is picking up. The question is whether to use it before or after neurostimulation, but it is a potentially significant threat to Medtronic's InterStim, especially if it gains FDA approval for this indication and the currently spotty reimbursement improves. ♦ Hospitals with one of Intutive Surgical's da Vinci robots are buying additional robots, and academic centers without a robot are getting one – mostly for urology but also to share with gynecology, in particular. Other hospitals without a robot do not feel competitive pressure to have one. Yet, interest in robots for GYN procedures is definitely growing, and GYN is helping to justify purchases of first, second, and third robots.

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AMERICAN UROGYNECOLOGIC SOCIETY (AUGS)

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The three hottest things at AUGS this year were: Intuitive Surgical's da Vinci, Allergan's Botox for refractory urge incontinence; and mini-slings for stress incontinence.

ROBOTIC SURGERY: INTUITIVE SURGICAL'S DA VINCI

Dr. Anthony Visco of Duke University, speaking at a session sponsored by Intuitive, warned physicians just starting to use the da Vinci robot that the first few cases will take a "long" time, adding, "I don't think you can dabble in robotics. You have to make a commitment to it. If I did this once in a while, I and my team would be frustrated." He recommended that, at least for their first five cases, new users choose women who are:

- Relatively thin (BMI <30).
- Healthy – age <60 with few comorbidities.
- No previous intra-abdominal or pelvic surgery.
- Reasonable-sized uterus, if present.

Dr. Arleen Song of the University of Michigan, speaking at a different session also sponsored by Intuitive, said there are several disadvantages to conventional laparoscopic gynecologic procedures including: Limited degree of motion within the body, hand movement that is counterintuitive, 2-D vision, unsteady image, lack of precision, and a significant learning curve for advanced cases. In contrast, she said the robot offers 3-D imaging and 7 degrees of movement that "mimics the human wrist movement."

But there are also disadvantages to the robot. Dr. Song cited: Lack of vaginal access, large footprint, cost, and haptic/tactile feedback, which she said can be challenging initially. She called the robot an "enabling technology to shorten the learning curves for advanced laparoscopic procedures and level the playing field between a novice and an expert."

Twenty-two doctors at AUGS were interviewed about the outlook for robotics in gynecology. It appears use by users is increasing, and users are buying additional robots, but hospitals without a current robot are not yet convinced of their value, and they don't feel pressured by competitor marketing or physician or patient demand to get one. The exceptions are major academic centers, which almost have to have a robot today to keep their leadership position and to train fellows.

Fourteen of these 22 sources already have at least one or more da Vinci robots at their hospital, and one hospital is about to install its first da Vinci. Of the 14

current da Vinci owners in this group, two do not use it at all for GYN yet. A doctor from one hospital where GYN doesn't use the da Vinci said, "Our GYNs do laparoscopic procedures well and quicker than the robot." The other also does a high number of laparoscopic procedures.

Initially, a robot was, for all but one of these sources, purchased for urology, and gynecology – and sometimes other areas – began to use it on a limited basis. Today, at all but one site, the existing robot(s) is shared by urology and gynecology – and sometimes with general surgery and/or cardiac surgery – and use by both urology and gynecology is increasing.

GYN use of the robot(s) varies substantially from institution to institution, but, on average, 22% of robot usage is for GYN procedures (range <5% to 50%). An Oregon doctor said, "GYN uses the robot only about 5%-7% of the time, with only a couple of doctors using it for GYN, but when we get another robot, we could get to 30% GYN use." A New York doctor said, "We are getting our first robot, and I expect GYN will use it 30% of the time, initially for hysterectomies and some pelvic organ prolapse surgeries. (GYN) Oncology will use it later."

GYN appears to have had little impact on the hospital's decision to buy the first robot – even after the da Vinci gained FDA approval for gynecologic procedures – but GYN is helping to justify the purchase of a second or third robot. Three current da Vinci users are considering adding a second robot, and three are considering a *third* robot over the next 6-24 months. Comments included:

- "We could justify another shared (with urology) robot."
- "We probably need a third robot. Even with two robots, a robot is only available to gynecology two days a week."
- "We are considering a second robot because it takes us six weeks to get on the schedule now, but it would not be dedicated to gynecology."
- "We are getting another robot because the room gets booked up with urology, but we will still share it with urology. GYN oncologists have just gotten credentialed on it, and they will use it more and more, especially for lymph node dissections."

However, not everyone is sold on the value of a da Vinci robot in gynecology. A South Dakota surgeon said, "I don't see a third robot. Some doctors who started on the bandwagon have stepped off. The enthusiasm for some users has waned." A Maryland doctor said, "Only two gynecologists used our robot, which is mainly used by urology, and one of these left and the other died, so no one is really an active user now. We don't use the robot to distinguish ourselves. A few patients ask about the robot, but it is not the reason they come to us."

Sources generally agreed that their hospital does not feel pressured by marketing considerations to get a robot. Many of the current robot users have other hospitals in their market with a robot, so they are not really able to distinguish themselves by having a da Vinci, and those who do not have a robot do not believe they are losing patients to hospitals that have a robot. Furthermore, hospitals with a robot don't believe they are taking patients from hospitals without a robot, particularly if the doctors at the non-robot hospital perform laparoscopic surgery.

Most of the 7 hospitals without a robot are smaller facilities. The one large academic center without a robot is debating the purchase of its first robot right now; while a decision hasn't been made, a doctor from there expects that they will get one – to share with urology. Another mid-size hospital is considering one, but a doctor from there said, "It is a big investment, and I feel no urgent need to get one."

Most hospitals without a robot do ***not*** plan to get one. A West Coast doctor said, "It is mostly a hospital cost issue. In most general GYN surgery, it is not necessary, though in very specialized cases it is helpful." An Alabama doctor said, "I refer some oncology patients to (a major medical center) that has a robot, but not for a robotic procedure…The robot is not a flash in the pan because it is established in urology, but it has yet to demonstrate its value in gynecology." A California doctor said, "They haven't shown me why we need one." A Nevada doctor said, "The robot's role is established in urology. Its role in gynecology is still vague and to be debated…especially when it takes three hours to do a procedure with the robot that you can do in 45 minutes laparoscopically. Other issues include cost and time under anesthesia. And we've had a couple of deaths or catastrophic complications in town…Our group is debating whether they want to get involved with the robot. It has an advantage in more delicate, intricate surgery, but the disadvantages are cost and complications."

Within gynecology, how is the robot used most often? Sources said the most common uses are: gynecologic oncology (cervical and uterine cancer and lymph node dissections), sacrocolpopexy (for pelvic organ prolapse), tubal anastomoses, myomectomy (uterine fibroid removal), and, least commonly, hysterectomies. Among doctors attending AUGS, the key application for the robot is sacrocolpopexy. Dr. Cheryl Iglesia said 40% of da Vinci use at Washington Hospital Center is for gynecology, "We use the robot in 75% of cancer cases, 50% of benign hysterectomies, and 10% of laparoscopic myomectomies."

Dr. Visco said he doesn't view robotic sacrocolpopexy as a new procedure, but the same procedure through minimal incisions. He cited several advantages to the robotic approach for treatment of pelvic organ prolapse, including:

- Better access to pelvis compared to open and laparoscopic approaches.
- Easy rectovaginal dissection.
- Easy pre-sacral dissection.
- Easy handling of the mesh.

- Can be combined with hysterectomy.
- Enables more meticulous, precise, and comprehensive dissection, surgery, and handling.

What are the benefits of the robot? Approximately 600,000 hysterectomies are performed in the U.S. annually, and 75% of them are performed via an abdominal approach, not laparoscopically. Laparoscopic hysterectomies have a high learning curve, and the hope is that the robot will increase the use of laparoscopic procedures. Doctors who already do laparoscopic procedures see little value in the robot for them – though many admit it will help other doctors begin doing laparoscopic procedures. Comments included:

- *South Dakota doctor with 2 robots:* "It is difficult to know if there is an advantage to the robot. With a straightforward laparoscopic hysterectomy, there isn't. But for patients with significant prolapse, when you do a sacrocolpopexy, it does provide an advantage. It is also good for tubal re-anastomoses and myomectomies…But the device has not increased safety or efficacy or given patients a quicker recovery."
- *Virginia doctor with 2 robots:* "I think the robot is great for sacrocolpopexies and tubal anastomoses, but it is hard to justify it for more common procedures like hysterectomies if you are already doing laparoscopic hysterectomies…It is also good for marketing. It is sexy."
- *Kentucky doctor with a robot:* "Learning to do a laparoscopic procedure is a long, steep learning curve. It is much less difficult to learn to use the robot. You can go straight from an open procedure to a robotic procedure, but I wouldn't recommend that…With the robot you see better, there is likelihood of significant bleeding, magnification is better, and there is more maneuverability."
- *Midwest doctor without a robot:* "I send patients to a GYN oncologist who was an outstanding laparoscopic surgeon before he got a robot, but some of his colleagues couldn't do some difficult cases that they can now do with the robot…For us the only advantage is it might make some procedures easier to do, but we are a small community hospital and have no plans to get a robot."
- *Washington DC doctor with a robot:* "It is so much easier to sew with the robot, and the robot is better than open procedures in some cases. For example, you can't sew backwards in an open procedure, and you can do that with a robot."
- *Oregon doctor with a robot:* "Any knot tying intraabdominally is where the robot has value…For oncology, the magnification is a big advantage, and it is good for dissection of small vessels and lymph nodes. I'm not sold yet on the robot, but I'm doing it. It takes me four hours to do a procedure with the robot vs. 2 hours laparoscopically."

What are the clinical benefits of the robot **to patients***?* Most sources agreed that there is little clinical benefit to patients of a robot, that most of the benefit is to the physician. However, some doctors pointed out that it is a patient benefit when the robot makes laparoscopic and minimally-invasive surgery available to more patients. A surgeon with a robot said, "There is no advantage to patients. The advantages are very limited, and there are no studies to show there is a patient- or safety-driven advantage. But there are surgeons who can now do laparoscopic procedures who couldn't technically do them before, who felt uncomfortable with a standard laparoscopic hysterectomy, who now have a comfort level with the robot." Other comments included:

- *Washington DC:* "Most of what we do robotically would have been an open procedure without the robot."
- *Virginia:* "It does make patients who were not candidates for a tubal anastomosis in the past – mostly because of obesity – eligible for the surgery, so it does open up the procedure for patients who were never candidates."
- *Kentucky:* "At this point, the advantage is theoretical."
- *Dr. Visco:* "There is a potential to increase the use of a minimally-invasive approach. A minority of hysterectomies are done laparoscopically now – about 10% in the U.S. – because it is harder than an open procedure. Fewer than 5% of sacrocolpopexies are done laparoscopically now."
- *Oregon:* "There is no patient benefit to the robot. There are actually fewer punctures with a laparoscopic procedure than with the robot…The robot is mainly urology-driven. I'm glad it is available, and I will use it more and more, but I saw two patients recently that I did with the robot, and they aren't doing as well as my laparoscopic patients."
- *New York:* "The robot helps with precision, and so the hope is that it will reduce complications. The robot is slower, and there is a learning curve, but once you are past that, I think it will be faster."

How is a laparoscopic hysterectomy different from a robotic hysterectomy? Dr. Visco said, "The robot has increased 3-D visual magnification, and there is greater dexterity of the instruments. The procedure itself is similar to laparoscopy."

Is the cost of the da Vinci consumables an issue with the hospital? Sources insisted it is not. They explained that the da Vinci consumables (called "reposables") can be used for 10 patients before replacement, and the costs were described as comparable to the consumable costs of laparoscopic surgery. All sources agreed that there has been no need to justify the consumable costs to hospital administrators.

Are patients aware of or asking for robotic gynecologic surgery? No. Surgeons said that ***some*** patients are aware of robotic surgery and inquire about it, but sources – both surgeons with a robot and those without – agreed that the

availability of robotic surgery is not affecting patient flow. That is, hospitals without a robot are not currently losing patients to hospitals with a robot, and hospitals with a robot do not believe the robot is increasing their patient volume. A Virginia doctor said, "Patients do ask about it and discuss it." A Kentucky doctor agreed, "Some GYN patients have heard about it." An Oregon doctor said, "Three other hospitals in my area have a robot, but no one loses patients by not having a robot for gynecology." A New York doctor said, "No patient has ever asked about it, not once." A North Carolina doctor said, "Patients aren't asking for the robot, but more and more patients want a minimally-invasive surgical approach."

STRESS URINARY INCONTINENCE (SUI)

More than 30 million Americans suffer from incontinence. The prevalence increases with age, to 30% of women age ≥75. Of this, 25% is stress incontinence and 20% urge incontinence. Mixed incontinence accounts for another ~35% and other forms for 20%. SUI is caused by a decreased urethral sphincter muscle function at the bladder outlet, resulting in accidental urine leakage. Thus, normal activities such as coughing, sneezing, lifting, or exercising can lead to an episode of incontinence.

Most SUI patients are either untreated or take oral medications. The surgical treatment for stress incontinence is a pubovaginal fascial sling. In these operations, doctors attach a piece of fascia (autologous, allogeneic, or cadaver fascia, or, most commonly, polypropylene mesh) around the neck of the bladder to keep in urine, even under stress.

From 220,000-300,000 surgical SUI procedures are performed in the U.S. annually, with 120,000-200,000 of these women getting a sling. Several companies also offer sling materials and systems. Dr. Matthew Barber of the Cleveland Clinic warned, "Not all slings are created equal." Dr. Mickey Karram of the University of Cincinnati said that most slings today use synthetic materials, "That is where the surgery is going in a very, very fast way."

Sling products

The three types of sling products – all using polypropylene mesh – for SUI are:

➢ ***First generation:*** **Tension-free vaginal tape.** Some people refer to this generically as TVT, but TVT is the brand name for **Johnson & Johnson/Ethicon/Gynecare's** product. Asked what the advantage of TVT is, Dr. Barber said, "***Theoretically***, you almost can't damage anything other than the bladder with TVT. Other than that, there probably isn't an advantage, and a lack of data is a disadvantage."

"Traditional" Sling vs. TVT

Measurement	"Traditional" sling	TVT
Placement	Bladder neck	Mid-urethra
Material	Variable	Polypropylene mesh
Arms	Sutured	No fixation
Tension	Variable	Tension-free
Performed	Inpatient	Outpatient
Mechanism	Reposition bladder neck, possibly urethral compression	Urethral kinking
Data	Substantial	Insufficient

➢ ***Second generation:*** **Transobturator slings.** Some people refer to this as TOT, but Boston Scientific trademarked the name T.O.T. (transobturator technique). Dr. Karram said, "They (TO slings) were quickly adopted, based on rare complications with TVT, without a lot of data on efficacy or safety…but they have been relatively safe and effective." Dr. Barber agreed that bladder injuries are rare with this approach, but they do occur, and hematomas are also rare but have been seen. He noted that there is a risk of obturator neurovascular injury, but no bowel or major vascular injuries have been reported yet.

Dr. Steven Kleeman of the University of Cincinnati said an Austrian registry found a 0.8% rate of groin pain with TOT, adding, "My personal experience is that it is self-limiting… and resolves in the first few days…The take-home message: You tend to have fewer complications with transobturator than retropubic…Vaginal extrusions seem more common with the transobturator approach, and infections are more common with transobturator, but bleeding complications and bowel injury are more common with retropubic slings."

➢ ***Third generation:*** **Mini-slings** – a "micro"-invasive approach. The slings are ~8 cm long and require only a small vaginal incision; the sling never gets to the muscles or structures of the inner thigh. AMS's MiniArc is FDA approved but is not generally available yet because it reportedly is being redesigned. The MiniArc has a self-fixing tip with a barb on it that is inserted into the obturator fascia. Dr. Karram said, "Theoretically, these slings, being totally isolated to this smaller area, may have a better safety profile." Dr. Barber said, "Other than bladder injury, injury to other organs is almost impossible" with this approach. It also has the potential to be done as an outpatient procedure. But he pointed out that there are no data yet on efficacy or safety, warning, "You will see these (mini-slings) pushed, but there are almost no data…I caution you to be cautious. I don't know if they work as well or not. We need to wait for large trials, and it will be 12-18 months before we have that data."

Dr. Iglesia of the Washington Hospital Center cited several unanswered questions, including:

- How do you balance surgical innovation with the need for timely evidence-based safety and outcome reporting? She called that a "million dollar question."
- Which approach is best for what patient?
- Who needs mesh augmentation?
- Which mesh is optimal? What is the balance between effectiveness and complications (erosions)?
- What are the long-term outcomes for prolapse procedures with and without mesh?

- Should a prolapsed uterus be suspended or removed?
- What is the role and cost-effectiveness of laparoscopic and robotic-associated sacrocolpopexy?
- When and which prophylactic anti-continence operation (Burch or sling) should be performed?
- Should an asymptomatic defect be corrected?
- What is the natural history of Stage 2 prolapse?

Sling usage

Ross Longhini, executive vice president and chief operating officer of AMS, said the sling market has shifted from TVT to transobturator, adding, "We sell more Monarc than Sparc now …The market is mostly transobturator." He estimated that transobturators (TO) slings now account for about 70% of the market. Among the 20 doctors questioned at AUGS about their choice of sling products, TVT still is more popular than TO, but TO use is increasing. Doctors estimated that 59% of their sling use is TVT-type slings, 36% transobturator slings, and 5% others.

Transobturator slings are continuing to gain popularity, and sources estimated that they will account for a slightly larger share of their use (to ~41%-46%) within a year. New data presented at the meeting by the Cleveland Clinic's Dr. Barber made some doctors much more comfortable with transobturator slings. He compared TVT to TOT in 170 women, with an

Physician Sling Usage by Brand

Usage share	Sling	Type
32%	J&J's TVT	TVT
14%	Boston Scientific's Lynx	TVT
13%	AMS's Sparc	TVT
20%	AMS's Monarc	TO
13%	J&J's TVTO	TO
3%	Boston Scientific's Obtryx	TO
5%	Other	Variety

Comparison of Commercial Sling Systems

Company	Brand	Notes	Type	Approach
AMS	Sparc	Safer because of approach, company relationships	TVT	Top-down
AMS	Monarc	Can do repeat procedure; maybe fewer complications than TVT	Transobturator	Outside-in
AMS	MiniArc	Minimally-invasive approach, doesn't break membrane like TO, easier to learn than competitors	Mini-sling	Inside-out
AMS	AdVance	Male sling	For men	Outside-in
CR Bard	Align	Self-anchoring. Same as Uretex but new trocar, new mesh, and manufactured by Bard itself	TVT	Either top-down or bottom-up
CR Bard	Align-TO	Self-anchoring. Same as Uretex but new trocar, new mesh, and manufactured by Bard itself	Transobturator	Outside-in
CR Bard	Uretex	Being phased out and replaced by Align-TO	Transobturator	Either top-down or bottom-up
Boston Scientific	Advantage	Pre-packaged, no assembly required, ability to rotate tape, heat sealed edges of tape in area near urethra stiffer	TVT, retropubic	Bottom-up
Boston Scientific	Lynx	Pre-packaged, no assembly required, ability to rotate tape, heat sealed edges of tape in area near urethra stiffer	TVT, suprapubic	Top-down
Boston Scientific	Obtryx	Pre-packaged, no assembly required, ability to rotate tape, heat sealed edges of tape in area near urethra stiffer	Transobturator	Outside-in
Caldera	T-sling	Stiffer mesh	TVT, retropubic, and transobturator	All approaches
Caldera	T-sling Xtra	Center portion of sling is flared out (1.65 cm wide) for more urethral support	TVT, TO, and retropubic	All approaches
Caldera	T-sling Centrasorb	Center portion of sling has PDS suture that dissolves in 10 days for surgeons worried about erosions	TVT, TO, and retropubic	All approaches
Caldera	Desara	Mesh keeps memory when put under 5# of force, has only posterior introducer for vaginal vault prolapse, only FDA-approved sling for vaginal vault prolapse	TVT, transobturator, and retropubic	All approaches
Coloplast	Supris	---	TVT	Top-down
Coloplast	Aris	Stiffer graft. Replaced Obtape	Transobturator	Top-down or bottom-up
Cook	Stratasis TF	Only FDA-approved biomaterial; natural, not synthetic material. Doesn't encapsulate, no erosions	TVT	Either top-down or bottom-up
Johnson & Johnson/ Ethicon/Gynecare	TVT	Most data, easier than Sparc in obese women, more variety of approaches. Easily deformed at low load but stiffer at higher loads.	TVT	Both bottom-up and top-down versions
J&J	TVTO	Clinical data, less-invasive approach, can assure mid-urethral placement, less dissection	Transobturator	Inside-out
J&J	TVT-Secur	More adjustable, absorbable tip	Mini-sling	Inside-out but doesn't come all the way out

average follow-up of 18.2 months, and found TOT was non-inferior to TVT. He said mean operating time, blood loss, and hospital length of stay were comparable in both groups. Time to development of any urinary incontinence was not significantly different with TOT vs. TVT. His conclusion was: The Monarc TOT is not inferior to TVT at 1-2 years. For this study Dr. Barber received an award for the best clinical paper at the meeting.

Comparison of TVT vs. TOT

Measurement	TVT (J&J TVT) n=88	TOT (AMS Monarc) n=82	p-value
Intraoperative complications	9%	1%	0.02
Bladder perforations	7%	0	0.02
Mesh erosions	5.6%	1.2%	Nss, 0.24
Leg pain	2.4%	4%	Nss
Primary endpoint: Abnormal bladder function	46.6%	42.7%	Nss *

*** Using standard statistical testing this was a non-significant difference; however, the p-value for non-inferiority was .006 supporting the conclusion that TOT was not inferior to TVT.**

Longhini said, "That was first-time, powerful, definitive data that maybe this (transobturator) should be first-line treatment, and I think we will see more shift to transobturator…TVT will never go away, but I think the market is shifting slowly to transobturator…We are probably on the cusp of the next revolution – to mini-slings. Less and less invasiveness is the intent…Anecdotally, a number of physicians are doing the MiniArc under a local anesthetic and doing it in 5-7 minutes with efficacy very similar to gold standard slings like Monarc and TVT." Liz Groover, director of marketing for AMS, added, "With this data, we could see another jump in procedure growth again…And new slings (mini-slings and male slings) could push growth again."

Doctor comments on sling choices included:

- *Missouri:* "I'm just starting to do transobturator slings with Obtryx because it was what I saw in training, and I think it makes the most sense in terms of leg pain."
- *Oklahoma:* "I use the AMS Monarc 80% of the time – because the sales reps are good, and there is no difference in slings."
- *New Jersey:* "I use J&J's TVT mostly, but now that there are two-year data on transobturator slings, I'm more comfortable with TOT. I was waiting for data. TVT seems to be showing some higher bladder perforation, but TOT had a 4% problem with thigh pain, even though that was not statistically significant. So the question is whether you are trading one problem for another. What I took away is that they are equivalent…Perhaps I'll do a little less TVT and a little more TOT over the next year, but just a small shift."
- *Kentucky:* "I'm more comfortable with up-down TVT, but I do transobturator slings in very obese patients. There are more bladder perforations with the down-up approach."
- *New York:* "I use only J&J's TVT – no TOT – because there is no long-term data on TOT. The Barber data is promising, but I'm not sure it will change what I do."
- *Wisconsin:* "I use TVT for 90% of procedures. I did TOT in the beginning, but I felt there were more erosions, and patients could feel them more often (with TOT)…The Barber data won't change what I use."

Few of these doctors are using mini-slings yet. They are interested in them but taking a cautious approach. Comments included:

- *New York #1:* "The new mini-slings are worth watching. I'm just starting to use them. I've tried both (J&J's TVT-Secur and AMS's MiniArc), and they are both good, but they are very different."
- *Missouri:* "There aren't much data yet, but I'm watching them."
- *Kentucky:* "I haven't tried mini-slings yet, and I'm not sure I will."
- *Oklahoma:* "I haven't tried a mini-sling yet, but I'm interested, and I probably will try the MiniArc."
- *New York #2:* "I don't see a reason to use mini-slings; TVT works."
- *Wisconsin:* "I have no interest in mini-slings."
- *Rhode Island:* "I haven't tried a mini-sling yet, but I want to try it."
- *Connecticut:* "I am waiting for data on the mini-slings. There are no data now. They (the mini-slings) are intriguing, but there are no problems with the old version. The Barber data are interesting…We may need to do TOT now. We have to talk about that when we get back home."
- *New Hampshire:* "The mini-slings are essentially double the cost, and there are no outcome data, so I'd be experimenting with patients, and I'm not going to do that."
- *Canada:* "I'm not ready for the mini-sling yet. I need to see long-term data."
- *Florida:* "We need more data. I'm not convinced, but I'm watching it. If it works, it would be great, but the physics behind it don't make a lot of sense."

Sling pricing and sales outlooks

Procedure volume remains steady, doctors insisted. However, procedure growth has slowed for the industry. AMS's Longhini said, "Growth rates (for the industry overall) are down. They were phenomenal at 40%-50% a year a few years ago as the marketplace was getting penetrated with slings.

Now, penetration is fairly high, so now growth rates more closely approach the demographic rate, which is about 3%. Slings are growing faster than that, but not 40%-50% a year."

Pricing has gotten ***very*** competitive. There are more competitors, low barriers to entry, and hospitals are more focused on sling prices. Most slings are priced at about $595, but there are so many deals, discounts, and contracts that almost no company could cite an "average" price for its sling products. Industry and physician sources alike agreed that there is a lot of dealing going on, making it hard to know the real price hospitals and doctors are paying for the devices. And the pricing situation is not expected to improve. AMS's Longhini said, "There are a lot of competitors out there now, and low barriers to entry." Groover added, "Hospitals are looking to bid more, and they are paying more attention to sling prices."

Yet, sales of slings may get a boost from three things:

1. New data on transobturator slings that show equivalence if not superiority to TVT.
2. Mini-slings.
3. Male slings.

Other options: Radiofrequency (RF)

Novasys Medical's Renessa is a less-invasive RF system for SUI. A transurethral probe reaches into the bladder neck and emits a low level RF that purportedly "remolds" the collagen and reduces incontinence. The device costs about $10,000 plus $1,000 per probe. The company claims that in studies 58% of women have eliminated the need for pads.

Reimbursement, when available, is about $2,600. But it can be a challenge and a hassle. There is no CPT code yet, and Medicare coverage reportedly varies by region. A company official says United Healthcare and Humana tend to pay for it, but Aetna does not, "Thirty-five percent of claims are being paid, but the claims have to be paper, and often it requires an appeal."

A company official insisted that Renessa makes sense when pharmacology fails and before a surgical procedure/sling. And the device seems appealing, but doctors at AUGS who were questioned about it were all extremely dubious. Many knew about the problems with an earlier invasive RF device – Cooper Surgical's SURx Radiofrequency Bladder Neck Suspension System, which was withdrawn from the market – and are worried about "cooking" tissue, creating scar tissue, or making future operations more difficult. One doctor said, "I saw a patient whose urethra was melted by the earlier RF system. Once you've seen that, you don't ever want to try RF again." Another commented, "I've never seen it done in clinical practice. I'm highly dubious. There are still no data on it." A New England doctor said, "Renessa looks like just a different version of SURx, which really didn't work."

Urologist Dr. Lindsay Kerr, who is on the Renessa advisory board, said, "The Renessa frequency can remold tissue. It is only a little more invasive than a pessary, which is significantly less invasive than about everything else. Once the reimbursement issue is solved, it will take off."

Pelvic Organ Prolapse

More than 200,000 American women have pelvic organ prolapse each year. An expert estimated that a woman runs an 11.1% lifetime risk for a surgical intervention for pelvic organ prolapse, and 29%-40% of reconstructive procedures require a surgical re-intervention for failure, with 60% of recurrences at the same site.

Prolapse repair materials

In February 2007, the American College of Obstetricians and Gynecologists (ACOG) issued a practice bulletin on pelvic organ prolapse, saying, "Given the limited data and frequent changes in the marketed products…the procedures should be considered experimental, and patients should consent to the surgery with that understanding."

Surgical Approaches to Pelvic Organ Prolapse

Surgery	Advantages	Disadvantages/complications
Abdominal sacrocolpopexy (ASC)	Lower rate of recurrent apical prolapse vs. SSLF. Reliably good cure rates. Considered by many to be the gold standard. Only 3.3%-8.8% erosion rate.	2.4% mesh erosion rate
Uterosacral ligament vaginal vault suspension (USLS)	Recurrent apical prolapse in 15%-31% of patients	Neural pain, small bowel injury, suture erosion. Concerns are durability and urethral injury.
Sacrospinous ligament fixation (SSLF)	Recurrent apical prolapse in 15%-31% of patients	Buttock pain, nerve or rectal injury, vaginal stenosis, stress incontinence, hemorrhage
Laparoscopic sacrocolpopexy	Less blood loss and shorter hospital stay than ASC	Longer procedure time than ASC, high level of technical skill required.
Robot-assisted laparoscopic sacrocolpopexy	Short hospital stay. Flexibility, learning curve easier than regular laparoscopy. Identical repair to ASC.	Cost, learning curve

Prolapse Repair Materials

Material	Advantages	Disadvantages
Autografts	Good outcomes in SUI surgery	Morbidity of 2nd surgical site
Cadaveric/ allogenic grafts	---	Poor outcomes in both sling and ASC
Xenografts (porcine, bovine)	---	Conflicting data; poor outcomes in ASC; Level I evidence that it is not beneficial for posterior repair
Absorbable synthetics (e.g., polyglactin)	Fibrosis disappears	Conflicting Level I evidence that it improves anterior repairs; effects on bladder/bowel function not known
Permanent synthetics	Superiority shown in trials and case series. Level I evidence that it is superior to cadaver fascia. Potentially more durable	---
Surgical mesh kits	Can correct multiple defects at one time. Interesting potential	Mesh erosions, *de novo* pain, *de novo* stress urinary incontinence, dyspareunia, cost. No "best" kit.

URGE INCONTINENCE (UI)

Anti-muscarinic therapy is the mainstay of therapy for urge incontinence, which is also called overactive bladder (OAB), but efficacy is less than ideal. In randomized clinical trials OAB medications have shown only a little more efficacy than placebo, which has a relatively high efficacy rate in these patients. The newest drug to treat urge incontinence is Indevus's Sanctura XR (trospium extended-release), which was recently approved by the FDA and will be launched in 2008. A speaker said, "If I sound pessimistic about our current approach to OAB, I am."

Newer Anti-Muscarinic Therapies for UI

Drug	Efficacy in RCTs (UUI/day) *	Comparator efficacy in RCTs
FDA-approved agents		
Astellas's Vesicare (solafenacin) 10 mg	62%	37% placebo
Indevus's Sanctura (trospium) 20 mg BID	58%	45% placebo
Novartis's Enablex (darifenacin) 15 mg	64%	47% placebo
Indevus's Sanctura XR (trospium extended-release)	60%	47% placebo
Investigational agents		
Schering-Plough's propiverine hydrochloride 20 mg QD	83.5%	61% solafenacin
Pfizer/Schwarz Pharma's fesoterodine 8 mg	87.5%	N/A
Kyorin Pharmaceutical's imidafenacin	Not a lot of studies yet	

* UUI = urge urinary incontinence

A speaker offered comments on other agents further away in the pipeline include:

- **PDE inhibitors** – "Experience in men with erectile dysfunction suggest there is some relief. PDE-1 and -4 are most important to the detrusor."
- **Beta adrenergic agents**. "The results are very mixed."
- Potassium channel openers. "Vascular side effects are a problem with the first-generation agents. (AstraZeneca's) ZD-0947 was no better than placebo at any endpoint (in a clinical trial). Is the target wrong, or is this not the right agent?"
- **Resiniferatoxin** (RTX), a capsaicin analog. "This is good in spinal cord injury but not OAB."
- **Cox-2 inhibitors**.
- **Tramadol**. "The primary adverse event is nausea (34% vs. 5.3% with placebo in one trial)."
- **Tachykinins/neurokinins**. "There were high adverse events in the one tested."
- **Alpha adrenergic agents**. "A recent randomized clinical trial found no benefit in OAB."
- **Gabapentin**. "There are significant adverse events."
- **Desmopressin**. "It has demonstrated usefulness in the treatment of children."
- **Magnetic therapy**. "There is insufficient evidence."
- **Acupuncture**. "There is insufficient evidence."

Neurostimulation

When patients fail drug therapy, there is one more FDA-approved option: neurostimulation. Currently, there is only one approved device, Medtronic's InterStim. A temporary lead and external generator can be used to test a patient before an InterStim is implanted, but Dr. Stephen Kraus, a neuro-urologist from the University of Texas Health Science Center at San Antonio, pointed out that efficacy can fade over time, and there can be side effects with the device, including pain at generator site (15.9%), infection (5.7%), lead migration (6%), though nerve damage or injury does not appear to be an issue.

Neurostimulation is being explored – but is not yet FDA-approved – for:

- Decreasing frequency and pain of interstitial cystitis.
- Chronic pain.
- Bowel control (fecal incontinence).
- Neurogenic bladder. "It has been shown effective in multiple sclerosis, but MRI is the problem," Dr. Kraus said.

In the future, technology advances are likely to lead to smaller generators, rechargeable generators, bilateral sacroneuro-modulation, pudendal stimulation, and cutaneous stimulation. Advanced Bionics' Bion implant was described as "kind of neat and sounded great, but unfortunately is going nowhere for now, based on industry funding issues." An industry source said, "I don't think Bion will ever see the market. I think it ran into a problem with recharging. The patient had to recharge every day, and patients didn't want to be reminded of their disease every day. They'd rather undergo a small surgical intervention to replace a battery every five years than be reminded every day by daily recharging."

AMS also has a neurostimulation device in development, and this is likely to give InterStim some real competition. AMS purchased Accessa from an Israeli company, BioControl Medical, and has since set up its own in-house neuro-electronics development team for Accessa.

AMS marketing director Groover said, "We are really excited about it, and we think a couple of things are really unique. With InterStim, the patient is placed on her stomach, and the lead is placed in the spinal column…which urologists are not necessarily trained to do…InterStim requires fluoroscopy and takes a great deal of time. With Accessa, the patient in placed in dorsal lorthotomy (the gyn exam position), which is a lot more familiar to physicians. There is no fluoroscopy. All you have to do is take a needle and make a slight incision next to the urethra, place the lead next to the urethra in the muscle of the urinary sphincter. The lead gets tunneled up in front of the

pubic bone to the device which sits in the abdomen. The placement of Accessa is simpler, more intuitive, and takes less time. And it stimulates the muscle instead of the nerve directly, so you have error room. One of the key things with InterStim is that if the lead moves, you have to reposition it or reprogram the device. Theoretically, there should be less patient management with Accessa." AMS COO Longhini added, "A lot of patients don't get treated or get treated somewhat with prescription drugs but not very effectively. Some get treated with Botox – which is increasing – but a lot of physicians are somewhat desperate for another solution and, frankly, an easier solution. We are seeing a lot of people not doing InterStim who say they would adopt an easier solution."

Unlike InterStim, Accessa's lead is not tined, so, theoretically, it might be easier to get out.

Accessa already has a C.E. Mark in Europe, but AMS is not selling it their yet while they collect data. Groover said, "In a live case in Europe, it took 10 minutes skin-to-skin (to implant it)." In the U.S., Accessa is currently in a pilot trial, and AMS expects to start a pivotal trial in 2008, but it probably won't be on the U.S. market until at least 2010. Pricing is likely to be comparable to InterStim.

Botulinum toxin (BTX)

Urologists have also started to use Allergan's Botox (botulinum toxin-A) off-label for OAB. Medicis's Dysport, another botulinum toxin-A, does not yet have FDA approval, and experts said not enough is known yet about Elan's Myobloc (botulinum toxin-B) to use it in urogynecologic disorders. Myobloc reportedly doesn't last as long as botulinum toxin-A, but it can work when BTX-A fails. In addition to OAB, BTX is being explored for interstitial cystitis (also called painful bladder syndrome), anal fissures, and myofascial pain.

Urogynecologists are also becoming interested in botulinum toxin therapy. There were talks at AUGS about it, and several doctors said they plan to start using Botox after the meeting. The question is which comes first after failed drug therapy: neurostimulation or Botox. One expert insisted that Botox should be reserved for patients who fail or refuse neurostimulation. A Medtronic source said it makes more sense to do InterStim first because you can do Botox one month after InterStim, but you have to wait at least six months after Botox to implant InterStim.

Dr. Sangeeta Mahajan of MacDonald Women's Hospital in Ohio said she offers both Botox and InterStim to patients and lets them make the choice, but so far most patients given the offer have chosen Botox. Asked what happens with the Botox failures, she said no Botox failures have gone on to neurostimulation, "They just gave up and dropped out of treatment."

Botulinum Toxin Therapy for Urge Incontinence

Measurement	Allergan's Botox	Medicis's Dysport	Elan's Myobloc
Type	A	A	B
Formulation	Vacuum-dried	Freeze-dried	Liquid formulation
Reconstitution pH	Neutral	Neutral	5.6

Dr. Mahajan offered some tips to doctors considering BTX use for OAB:

- Check the price at different sources. At her hospital pharmacy, Botox costs $1,200-$1,500 per procedure, but if she writes a prescription and the patient purchases it at the local pharmacy, the cost is about $600. Another doctor noted that Botox is available through Medco for $240.
- It takes 7-10 days to see the full effect.
- BTX is a good option for catheter-dependent women.
- The effect with 100 U, which is her usual starting dose (diluted in 20 cc of saline), lasts about 3 months. 200 U lasts longer than 100 U, and the maximum dose for detrusor treatments is 300 U. For spinal cord injury patients, she usually uses 300 U. She noted, "Higher doses (200 U and 300 U) last longer, but there is more retention."
- The pain of the Botox injection is "comparable to a periurethral collagen injection but tolerable."
- Insurance reimbursement is an issue. She said Aetna and a few other insurance companies cover it, but most patients pay out-of-pocket, "Most patients are willing to pay for Botox to avoid an implanted device."
- The data are mixed for BTX use in painful bladder syndrome, but she definitely feels there is a role for it there, commenting, "What do you lose with trying except a little retention?"
- If 200 U are used, you should wait at least 2 months before injecting Botox again, but if 100 U are used, you don't have to wait that long to re-inject.
- About 15% of patients have some retention after a Botox injection.
- She hasn't done many repeat injections with the same patient yet, but she said, "Most patients who do well the first time, do well the second time. You can do repeat injections until it stops working. Just repeat it at 6-12 months when the problem recurs."

Dr. Linda Brubaker of Loyola University reported the results of the NIH-sponsored RUBI study of Botox for refractory urinary urge incontinence. The primary endpoint was time to failure – Patient Global Impression of Improvement (PGI-I) – score ≥4 at least 2 months after the first injection or the commencement of any new treatment at any time after the first injection. This multicenter, randomized trial compared 200 U Botox to placebo. She concluded that Botox is effective in improving the symptoms of refractory urge incontinence in ~60% of the women

treated, with a median duration of effect of at least 6 months. However, urinary retention was common and required routine PVR (post-voiding urine residual) assessment.

Results of RUBI Trial of Botox for Urge Incontinence

Measurement	Botox n=28	Placebo n=15	p-value
Primary endpoint: PGI-I ≥4	N/A	N/A	<.05
Median time to failure	193 days	62 days	---

Another researcher also presented a study showing Botox effective in reducing urge incontinence episodes and improving quality of life – but at the price of some prolonged urinary retention requiring catheterization. Dr. Michael Flynn from the University of Rochester presented the short-term outcomes of a randomized, double-blind, placebo-controlled trial of Botox 200 U and 300 U for the management of severe idiopathic detrusor overactivity incontinence that was done at his center and at Duke. Interestingly, the two sites had slightly different protocols. Those differences were in inclusion criteria, duration of the placebo portion of the study before patients could crossover to Botox, and the volume and concentration of Botox used; Duke researchers diluted the Botox into 6 cc of saline, and the University of Rochester diluted it with 3 cc of saline. However, Dr. Flynn said he saw no differences in outcomes based on the dilution differences.

Results of Botox in Severe Idiopathic OAB

Measurement	Botox n=31	Placebo n=10
3-week results		
Change from baseline in incontinence episodes per day at 3 weeks	No change (p=Nss)	Reduced (p<.0001)
Quality of life at 3 weeks vs. baseline	No change (p=Nss)	Improved (p<.0001)
Adverse events at 6 weeks		
Urinary retention	0	19.4%
Urinary tract infections	30%	16% *

*** Likely due to prophylactic use of antibiotics.**

SPECIFIC COMPANIES: AMERICAN MEDICAL SYSTEMS (AMS)

What is AMS excited about?

➢ **AdVance**, a new transobturator sling for men post-radical prostatectomy launched late last year. Longhini said the company is "starting to build clinical data through this year, showing very, very good results." The advantage of this sling over AMS's InVance sling is InVance is anchored with bone screws and with AdVance there are no bone screws; it is self-fixating. Longhini added, "InVance is more of a compressive band while AdVance is more a repositioning instrument."

➢ **HerOption**, a cryotherapy system for treating menorrhagia (excessive menstrual bleeding) without a hysterectomy. Longhini said this is doing quite well, "It is geared to an in-office environment, and that is kind of a slow-to-develop marketplace, but we continue to slowly develop that market."

Competitors include Hologic/Cytec's NovaSure, which is the market leader in hospitals. AMS claims that in the GYN office, HerOption shares market leadership with NovaSure. He said Johnson & Johnson's ThermaChoice is "declining rapidly." What will happen to NovaSure under Hologic? Longhini said, "It is hard to know what will happen strategically with that marriage…It is an odd marriage."

➢ **Apogee and Perigee, for female pelvic prolapse.** Apogee is for retrocele and enterocele repairs and vault prolapse repairs, while Perigee is for cystocele repair. These were first approved in the summer of 2004, and they have undergone several iterative improvements since then. This year AMS made the Perigee needle longer, improved on the mesh (making the fiber slightly smaller, resulting in softer and more pliable mesh). Groover said it was launched a month and a half ago and the response is "really, really positive." She predicted, "As the data build, I think we will see more and more doctors looking to adopt these procedures."

➢ **Ovion, a sterilization system in clinical trials.** This is similar to Conceptus's Essure. It requires no external energy. With Ovion, a stent with a plastic, gauze-like material that is designed to encourage fibrosis across the stent, is placed with a small catheter into the fallopian tube. Groover said the advantage of Ovion is that it can be placed through a very small diameter, flexible hysteroscope or a rigid hysteroscope, "It is a smaller diameter delivery device, so it is more suited to doing the procedure easily in the physician's office. If you use a flexible scope, you don't have to manipulate the cervix to get to the left and right sides. You only have to go through the cervix once, instead of twice, so there is limited pain, and you can do it easily and quickly in the office." Cytec also has a minimally-invasive device, but it requires an RF generator.

Asked what AMS is depending on for sales growth in 2008, Longhini said, "AdVance, MiniArc, and some of the new prolapse procedures we are coming out with next year – (though he wouldn't say more about what they are). That is what will drive growth for the company…Beyond that, Accessa and Ovion are important."

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