Update on Surgical Mesh for Stress Urinary Incontinence (SUI)

FDA Meeting of the Obstetric and Gynecologic Devices Panel
September 9, 2011
Introduction

Jeff Secunda
Vice-President, Technology & Regulatory Affairs
AdvaMed
Stress Urinary Incontinence (SUI)

- Common and often debilitating condition
- Mid-urethral slings
  - Safe, effective, less invasive procedure
  - Less pain
  - Quick return to regular activity
510(k) Process

- All mid-urethral slings for SUI have been brought to market under 510(k) process
  - Process works
  - Allows for medical advances to occur
# Agenda

| Unmet Medical Need | Suzette E. Sutherland, MD  
| Surgeon, Metro Urology  
| Adjunct Associate Professor  
| University of Minnesota |

| Clinical Overview | Piet Hinoul, MD, PhD  
| Director, Medical Affairs  
| Ethicon Women’s Health and Urology |

| Regulatory Pathways | Ginger Glaser  
| Sr. Director, Global Quality & Regulatory Affairs  
| American Medical Systems |
Unmet Medical Need

Suzette E. Sutherland, MD

Metro Urology
Centers for Continence Care and Female Urology
The Pelvic Floor Center
Adjunct Associate Professor, Dept. of Urologic Surgery, University of Minnesota
Stress Urinary Incontinence (SUI) Patient Profile

- Typical age range
  - 40-60 years old
- Physically active with young children
- Use of protective pads or diapers
- Avoids seeking treatment
Earlier Treatment Optimal

- Woman healthier with fewer concomitant issues
- Benefits all ages
Standard of Care
Mid-Urethral Sling
Clinical Experience Presented at ICS/IUGA Meeting 2010

- 367 consecutive single incision slings
- 91% subjective cure @ 12 mo
- 92% objective cure @ last follow-up
- Statistically significant improvements
  - UDI-6, IIQ-7, QOL, PISQ-12
- 2.7% (10 patients) sling revision due to obstruction
- No mesh-related erosions, extrusions, infections
- No-to-minimal pain reported at 2 weeks
- No dyspareunia related to sling
<table>
<thead>
<tr>
<th>TRADITIONAL SURGERY</th>
<th>MID-URETHRAL SLINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>More involved procedure</td>
<td>Easier procedure</td>
</tr>
<tr>
<td>1 hour +</td>
<td>15 – 20 minutes</td>
</tr>
<tr>
<td>Hospitalized 1 – 2 nights</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Pain along incision</td>
<td>IV sedation/local</td>
</tr>
<tr>
<td>Post-operative catheter</td>
<td>Less risk, less pain</td>
</tr>
<tr>
<td>Longer recovery period</td>
<td>Equally or more effective</td>
</tr>
<tr>
<td></td>
<td>Return to daily routine within 24 hours</td>
</tr>
</tbody>
</table>
Mid-Urethral Sling for SUI

- Very effective
- Long-lasting repair
- Complications are rare
Complications with Mid-Urethral Slings

- Risk of exposure decreases with surgeon experience
- Most complications can be easily treated
  - Topical estrogen application
  - Minor surgical excision
- Dyspareunia usually related to superficial placement
Complications with Traditional Burch/Bladder Neck Suspensions

- Greater interoperative bleeding
- Greater risk of bowel/bladder injuries
- DVT/PE
- Abdominal wound healing complications
- Greater post-op voiding dysfunction
- More post-operative pain
Great progress in SUI treatment

Transvaginal mid-urethral sling surgery
  - Is safe and effective
  - Has a long-lasting effect on a patient’s life
Safety & Efficacy

Piet Hinoul, MD, PhD
Director, Medical Affairs
Ethicon Women’s Health and Urology
Evolution of SUI Devices

1961
Evolution of SUI Devices

1961

1996
Evolution of SUI Devices

1961 1996 2001
Evolution of SUI Devices

Mid-Urethral Slings

- 800+ publications in the past 15 years
- RCTs and observational studies show superiority of mid-urethral slings vs. old gold standard
- > 2,000,000 women successfully treated with slings
# Cochrane Database Findings

## Mid-urethral Sling vs. Colposuspension

<table>
<thead>
<tr>
<th>Study</th>
<th>MISO (n/N)</th>
<th>Open Colpo (n/N)</th>
<th>Risk Ratio (M-H, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bai 2005</td>
<td>27/31</td>
<td>29/33</td>
<td>0.99 (0.82, 1.19)</td>
</tr>
<tr>
<td>Drahoradova 2004</td>
<td>75/79</td>
<td>59/60</td>
<td>0.97 (0.91, 1.03)</td>
</tr>
<tr>
<td>El-Barky 2005</td>
<td>18/25</td>
<td>18/25</td>
<td>1.00 (0.71, 1.41)</td>
</tr>
<tr>
<td>Sivaslioglu 2007</td>
<td>42/49</td>
<td>43/51</td>
<td>1.02 (0.86, 1.20)</td>
</tr>
<tr>
<td>Wang 2003</td>
<td>45/49</td>
<td>38/41</td>
<td>0.99 (0.88, 1.12)</td>
</tr>
<tr>
<td>Ward 2002</td>
<td>103/159</td>
<td>90/127</td>
<td>0.91 (0.78, 1.07)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>392</td>
<td>337</td>
<td>0.96 (0.90, 1.03)</td>
</tr>
</tbody>
</table>

- Heterogeneity: $\chi^2 = 1.17$, df = 5 ($P = 0.95$); $I^2 = 0.0\%$
- Test for overall effect: $Z = 1.08$ ($P = 0.28$)
Landmark RCTs

- TVT: 175 women
- Burch: 169 women
TVT vs. Colposuspension Study

Percentage “Cured” at 6 months
(by outcome measure)

- Neg Pad Test
- Neg Cystometry
- Obj Cure (Pad&Cysto)
- Never Leak
- No Stress Leak
- Patient Satisfaction

Week and Hilton, 2000
Landmark RCTs

Both procedures provide long-term effect on incontinence and improvement in QoL

Vaginal wall prolapse more frequent after Burch-colposuspension
Landmark RCTs

- 597 women randomized
- Objective success
  - 81% (retropubic) vs. 78% (transobturator)
- Subjective success
  - 62% (retropubic) vs. 56% (transobturator)
### RCT Cure Rates for Mini-Slings

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-Up (months)</th>
<th>Single-incision Mini-Slings n/N (%)</th>
<th>Mid-urethral Slings n/N (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basu 2010</td>
<td>6</td>
<td>22/37 (59.5%)</td>
<td>31/33 (93.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hinoul 2011</td>
<td>12</td>
<td>81/97 (83.5%)</td>
<td>96/98 (98.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tommaselli 2010</td>
<td>12</td>
<td>31/37 (83.8%)</td>
<td>31/38 (81.6%)</td>
<td>0.801</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>134/171 (78.4%)</strong></td>
<td><strong>158/169 (93.5%)</strong></td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*Cochran-Mantel-Haenszel procedure*
# Mini-Sling Outcomes in 2010

<table>
<thead>
<tr>
<th>Mini-sling</th>
<th>Study</th>
<th>Patients (n)</th>
<th>Objective Cure (%)</th>
<th>Subjective Cure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVT-Secur</td>
<td>Lim 2010</td>
<td>42 U</td>
<td>58.2</td>
<td>51.3</td>
</tr>
<tr>
<td></td>
<td>Khandwala 2010</td>
<td>128 H; 13 U</td>
<td>-</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Gagnon 2010</td>
<td>23 H; 25 U</td>
<td>-</td>
<td>69; 100</td>
</tr>
<tr>
<td></td>
<td>Liapsis</td>
<td>43 H; 39 U</td>
<td>62.8; 71.8</td>
<td>60.5; 69.2</td>
</tr>
<tr>
<td></td>
<td>Kim</td>
<td>62 H; 53 U</td>
<td>87.1; 88.7</td>
<td>82.9; 83.7</td>
</tr>
<tr>
<td></td>
<td>Lee</td>
<td>141 H; 144 U</td>
<td>80.1; 87.5</td>
<td>75.7; 77.1</td>
</tr>
<tr>
<td></td>
<td>Jeong</td>
<td>31 TVT-S; 33 TOT</td>
<td>71.0; 84.8</td>
<td>80.6; 78.8</td>
</tr>
<tr>
<td></td>
<td>Tommaselli</td>
<td>37 TVT-S; 38 TVT-O</td>
<td>83.8; 81.6</td>
<td>10.8; 13.1</td>
</tr>
<tr>
<td>MiniArc</td>
<td>Kennelly</td>
<td>157</td>
<td>90.6</td>
<td>87.3</td>
</tr>
<tr>
<td></td>
<td>De Ridder</td>
<td>75 MiniArc; 56 Monarc</td>
<td>85; 89</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Pickens</td>
<td>120</td>
<td>-</td>
<td>94</td>
</tr>
<tr>
<td>AJUST</td>
<td>Meschia</td>
<td>102</td>
<td>91.4</td>
<td>85.7</td>
</tr>
</tbody>
</table>

Kennelly M, Curr Urol Rep, 2011
Rise in Urogynecologic Services

Expected rise in urogynecologic services of 45% in the next two decades, whilst the population expansion is projected to be only 22% in that time period.

# Mini-Sling Peri-Operative AEs

<table>
<thead>
<tr>
<th></th>
<th>TVT-O</th>
<th>TVT-S</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Blood Loss (mL)</td>
<td>59</td>
<td>74</td>
<td>0.02</td>
</tr>
<tr>
<td>Peri-operative Complications</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding &gt;100cc</td>
<td>19%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Bleeding &gt;500cc</td>
<td>1%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cystotomy</td>
<td>0</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Vaginal Perforation</td>
<td>0</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Transfusion</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Hinoul, J Urol 2011
Evolution of SUI Devices
Conclusions

- Mid-urethral slings are well-understood
  - Mechanism of action
  - Mesh properties and mesh-specific morbidities
  - Impact of learning curve
Regulatory Pathway

Ginger Glaser
Sr. Director, Global Quality & Regulatory Affairs
American Medical Systems
FDA Questions

- (1.b) Given the incidence and severity of the adverse events, is there reasonable assurance of the safety of suburethral slings for SUI?
  - Yes

- (1.c) Does the clinical benefit outweigh the risk associated with the use of mesh suburethral slings?
  - Yes
Definitions

- **Safety**
  - Probable benefits outweigh the probable risks

- **Effectiveness**
  - Significant portion of the target population experiences clinically significant results
Reasonable Assurance of Safety & Effectiveness

- 7000 patients
- As effective as traditional fascial slings
  - Risk ratio 1.03, 95% CI (0.94-1.13)
- As effective as Burch colposuspension
  - Risk ratio 0.96, 95% CI (0.90-1.03)

Cochrane Report, 2011
FDA Question

(1.d) Should future premarket submissions for mesh products indicated for female SUI be supported by clinical performance data?

- Per FDA guidance

Final FDA Clinical Guidance, 2011

Guidance for Industry and Food and Drug Administration Staff
Clinical Investigations of Devices Indicated for the Treatment of Urinary Incontinence

Document issued on: March 8, 2011
The draft of this document was issued on September 19, 2008.
(1.d note) If FDA requires premarket clinical study with a control arm of traditional repair without mesh, reclassification may be necessary?

- Reclassification not necessary
FDA Question

(1.e) Should manufacturers conduct post-market surveillance studies on currently marketed first generation suburethral slings?

- No
(2.a) Is there adequate safety and effectiveness data on suburethral mini-slings?
- Yes

Mini-Sling study outcomes
- Adverse events as low as first generation slings
- Recent efficacy rates are 85 – 90%
FDA Question

- (2. b) Should future premarket submissions for mini-slings be supported by clinical performance data?
  - Per FDA Guidance

- (2.b note) If FDA requires premarket clinical study with a control arm of traditional repair without mesh, reclassification may be necessary
  - Reclassification not necessary
(2.c) Should manufacturers conduct post-market surveillance studies on currently marketed mini-slings?

- No
Conclusion

- SUI mesh is safe and effective
- 522 studies are not needed for existing products
- Clinical requirements can be managed via existing SUI guidance for future products
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