FDA Perspective on Surgical Mesh for Stress Urinary Incontinence (SUI)

September 9, 2010
Gaithersburg, MD
FDA Overview - SUI

• MDR Analysis
• Systematic Literature Review
• Clinical Overview
• Concluding Remarks and Panel Questions
Analysis of MDR Reports Associated with the Use of Surgical Mesh for SUI Repair

Presented by:
Nancy Pressly
Associate Director
Division of Postmarket Surveillance
Office of Surveillance and Biometrics

Analysis performed by:
Nasrin Mirsaidi, RN, MSN
Division of Postmarket Surveillance
Office of Surveillance and Biometrics

September 9, 2011
Gaithersburg, Maryland
Outline

• Overview of Medical Device Reporting (MDR)
• Search Methodology
• Limitations
• Results
What is MDR?

- MDR refers to Medical Device Reporting
  - Required under 21 CFR Part 803
  - Manufacturers are required to report deaths, injuries and malfunctions related to their devices to FDA.
  - User Facilities are required to report medical device related deaths to FDA and the manufacturer and Injuries to the manufacturer.
  - The MDR regulation is a mechanism for FDA and manufacturers to identify and monitor significant adverse events involving marketed medical devices.
Voluntary Reporting

• Anyone can file a voluntary report through FDA’s MedWatch program

http://www.fda.gov/Safety/MedWatch/default.htm
• Mandatory and Voluntary reports are entered into the Manufacturer and User Facility Device Experience (MAUDE) Database

• In 2010, FDA received more than 300,000 reports covering all medical devices
MDR Reports

• Provide a qualitative snapshot of adverse events for a specific device or device type

• Vary in quality and usefulness due to the information provided

• Include both problem codes as well as narrative text

• May be coded with multiple problem codes
Limitations of MDRs

• Under reporting of events
• Insufficient or inadequate information
• Inability to establish causality
• Inability to establish rate of adverse events
• “Trends” in numbers should be interpreted cautiously
Methodology

• Search Criteria
  – Product Codes FTL & FTM
  – Date Entered Between Jan 1, 2008 and Dec 31, 2010

• The following MDRs were removed:
  – Non-urogyn meshes,
  – Duplicate reports,
  – Reports with unknown device specifications,
  – Miscoded reports
Methodology (cont.)

• Remaining meshes sorted into POP or SUI
  – Based on the indicated use of the product reported

• Analysis completed using semantic text mining techniques as well as traditional analytical methods
Limitations Specific to this Search

• Multiple procedures in one operation
• Multiple meshes used
• Voluntary reporters used layman terminologies
# MDR Reports for SUI

<table>
<thead>
<tr>
<th>Year</th>
<th># of Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>368</td>
</tr>
<tr>
<td>2009</td>
<td>513</td>
</tr>
<tr>
<td>2010</td>
<td>490</td>
</tr>
<tr>
<td>Total</td>
<td>1371</td>
</tr>
</tbody>
</table>

* Previous time period – 2005-2007 approx. 835 reports
## Death Reports n=3

<table>
<thead>
<tr>
<th>Age</th>
<th>Summary of Report’s Narrative</th>
<th>Type of Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>73</td>
<td>Bowel perforation &amp; adhesion – died next day</td>
<td>Mid-Urethral Sling</td>
</tr>
<tr>
<td>UNK</td>
<td>Bowel Perforation – died of toxic shock and cardiac arrest</td>
<td>Sling Procedure</td>
</tr>
<tr>
<td>61</td>
<td>Erosion &amp; bleeding; on life support after mesh removal; died after life support discontinued</td>
<td>Sacrocolpopexy &amp; Sling Procedure</td>
</tr>
</tbody>
</table>
# Top 10 Adverse Events for SUI Reports

<table>
<thead>
<tr>
<th>Rank</th>
<th>Adverse Events</th>
<th># of MDRs</th>
<th>Percentile Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pain</td>
<td>479</td>
<td>34.9%</td>
</tr>
<tr>
<td>2</td>
<td>Erosion</td>
<td>436</td>
<td>31.8%</td>
</tr>
<tr>
<td>3</td>
<td>Infection</td>
<td>260</td>
<td>18.9%</td>
</tr>
<tr>
<td>4</td>
<td>Urinary Problems</td>
<td>220</td>
<td>16.0%</td>
</tr>
<tr>
<td>5</td>
<td>Organ Perforation</td>
<td>110</td>
<td>8.3%</td>
</tr>
<tr>
<td>6</td>
<td>Recurrence, Incontinence</td>
<td>103</td>
<td>7.5%</td>
</tr>
<tr>
<td>6</td>
<td>Bleeding</td>
<td>103</td>
<td>7.5%</td>
</tr>
<tr>
<td>8</td>
<td>Dyspareunia</td>
<td>73</td>
<td>5.3%</td>
</tr>
<tr>
<td>9</td>
<td>Neuro-muscular problems</td>
<td>50</td>
<td>3.6%</td>
</tr>
<tr>
<td>10</td>
<td>Vaginal scarring</td>
<td>22</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

*Total number of adverse events is larger than total number of MDRs because the majority of MDRs reported more than one adverse event*
## Most Frequently Reported Required Interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional Surgical Procedure</td>
<td>394</td>
</tr>
<tr>
<td>Partial or complete mesh explant</td>
<td>162</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>58</td>
</tr>
</tbody>
</table>
Summary

- Persistent signal related to the use of surgical mesh for SUI
- Serious, life-altering adverse events associated with the use of surgical mesh for SUI continue to be reported
Epidemiological Overview of Published Literature on Stress Urinary Incontinence and Need For Post-Approval Studies

Cara Krulewitch, CNM PhD FACNM
Branch Chief
Division of Epidemiology
Office of Surveillance and Biometrics
September 9, 2011
Outline

• Background
• Methods
• Findings
• Postmarket Regulatory Options
Background

• FDA purpose of reviewing the literature
  – Increase in adverse event reports

• Objectives of the FDA literature review
  – POP presented yesterday
  – Focus today SUI
Methods

• Medline database search on the treatment of SUI using surgical mesh
  – RCTs
  – Observational studies

• Time frame January 1996 to April 2011
Inclusion Criteria

• RCT any sample size

• Observational Studies
  – Multiple (at least one mesh) cohorts
    • Total ≥ 100
  – Single mesh cohorts
    • Total ≥ 50
Medline Search
Time frame: Jan1996-April 2011
(N=925)

RCTs, Observational studies, meta-analysis
(N=445)

Titles and abstracts reviewed for SUI and POP indication
(N=275)

• RCTs (82)
• Observational studies (105)
• Systematic reviews and meta-analysis (13)
(N=200)

Excluded (N=480)
Non-RCT, Observational studies sample size <50 per treatment arm

Excluded (N=170)
Non-clinical and cost-analysis studies, case reports, practice guideline, All non-systematic reviews and meta-analysis
Methods

• Title and abstract review of RCTs indicated many methodological limitations
  – Unmasked studies
  – Confounding
  – Non-hypothesis driven trials
  – Differential loss to follow-up
• Variations in measures of effectiveness
• Patients from observational studies and RCTs were grouped together safety only
Methods-Weighted Mean Averages

Percentage occurrence of each adverse event (AE) within a study treatment group or “cohort” was calculated for each time period as follows:

\[
\frac{\text{# patients with AE}}{\text{# patients within treatment group}}
\]

The percentages for each timeframe were then averaged across cohorts, weighting the percentage in each cohort according to the number of patients in the cohort.
Treatment Cohorts

- There were 391 treatment cohorts that met inclusion criteria for SUI
  - Range of treatment cohorts 1 to 3
  - Range of sample sizes in each treatment cohort 10 to 2795
Number of Surgical Mesh Treatment Groups/Cohorts by Surgical Procedures for the Perioperative Period N=391

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Number of Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVT</td>
<td>148</td>
</tr>
<tr>
<td>TOT</td>
<td>63</td>
</tr>
<tr>
<td>TVT-O</td>
<td>30</td>
</tr>
<tr>
<td>Other Sling</td>
<td>16</td>
</tr>
<tr>
<td>Pubovaginal Sling</td>
<td>10</td>
</tr>
<tr>
<td>Other where number of studies &lt; 10*</td>
<td>36</td>
</tr>
</tbody>
</table>

*Includes SPARC (8), IVS (6), **Mini-Sling (5)**, TVT or TOT (5), Burch with mesh (4), Other (8)
Number of Surgical Mesh Treatment Groups/Cohorts by Surgical Procedures and Follow-up Period in Months

Length of Follow-up (Months)

Number of Treatment Cohorts

- TVT
- TOT
- TVT-O
- SPARC
- Pubovaginal Sling
- Mini-Sling
- Other Sling
- Other SUI
- IVS
- Burch with Mesh
- TVT or TOT

- 6 (N=89)
- 12 (N=19)
- 24 (N=19)
- 36 (N=11)
- 48 (N=6)
- 60 (N=5)
Most Commonly Reported Adverse Events

- Erosion
- *de novo* dyspareunia
- Infection (including UTI)
- Pain
- Urinary problems
  - *de novo* SUI
  - Urgency, frequency and overactive bladder
  - Re-surgery
Most Common Peri-operative Complications

- Hemorrhage/Bleeding* (31.7%)
- Pain (6%)
- Infection (5%)
- Organ perforation (3.9%)
- Hematoma (1.0%)

*The definitions for hemorrhage or bleeding were disparate across the literature, and any conclusions to its clinical significance cannot be made.
## Reported Adverse Events at Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Range of Weighted Mean Percentages (%)</th>
<th>Range of Follow-Up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erosion</td>
<td>0.25 - 4.1</td>
<td>6 - 48</td>
</tr>
<tr>
<td>Resurgery</td>
<td>2.6 - 6.2</td>
<td>6 - 24</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>0.6 - 13.7</td>
<td>6 - 60</td>
</tr>
<tr>
<td>Pain</td>
<td>1.6 - 22.2</td>
<td>6 - 60</td>
</tr>
<tr>
<td>Urinary Problems</td>
<td>7.9 - 16.2</td>
<td>6 - 60</td>
</tr>
<tr>
<td>Infection*</td>
<td>4.8 - 27.4</td>
<td>6 - 60</td>
</tr>
</tbody>
</table>

* includes urinary tract infection

**NOTE:** Insufficient information exists in literature to provide quantitative measures of these adverse events among women with “non-mesh” surgeries
Weighted Mean Percentages Of AE Across Literature For The Treatment Of SUI Using Mesh Procedures By Follow-up Period

- Hematoma
- Bleeding
- Neuromuscular
- Erosion
- Pain
- Hemorrhage
- Dyspareunia
- Resurgery
- Urinary problems
- Infection

Length of Follow-up (Months) and Number of Treatment Groups:
- 6 (n=89)
- 12 (n=19)
- 24 (n=19)
- 36 (n=11)
- 48 (n=6)
- 60 (n=5)
Conclusions

• There were a number of long-term adverse outcomes

• Some higher at later time points up to 60 months

• Fewer treatment cohorts to evaluate after 36 months
Mini-Sling Findings

• Adverse events reported for second generation synthetic slings or “single incision mini-slings”
  – Greater intraoperative blood loss
  – Lead to higher rates of vaginal mesh erosion compared to first generation slings
Limitations of Literature

- Literature on SUI includes a variety of approaches
- Lack of statistical power for many studies
- Comparators vary for effectiveness measures
- Evaluator masking not present
- Many studies involve concomitant surgical procedures
- Adverse event reporting is inconsistent across the studies and not the focus for many studies
- Inclusion/exclusion criteria are incompletely documented
- Length of follow-up varies
- Causality cannot be determined
Postmarket Studies

We believe postmarket studies are warranted and can help more immediately answer questions regarding the long term safety and effectiveness of vaginal mesh used for SUI repair already on the market.
Need of Postmarket Studies

• Available scientific literature raises concerns of long-term safety profile for all SUI procedures

• Little scientific evidence for mini-slings (5 treatment cohorts)

The panel will be asked to consider whether postmarket studies are needed for cleared mini-slings, or all cleared surgical mesh indicated for SUI, and if so, should it be for all or a subset of these devices.
Design Options Available For 522 Studies Of Mesh For SUI

• May recommend RCT or prospective cohort study design that compares the device(s) to a control

• Sponsors responsible for study plans
  – RCT
  – Prospective cohort
  – Single sponsor registry
  – Multi-sponsor or society registry
  – RCT nested in registry
522 Recommendations

• Women 18 or older
• Documented SUI
• Surgery is scheduled
• Adjustment for pertinent risk factors
Safety and Effectiveness of Suburethral Mesh Slings for Surgical Repair of Stress Urinary Incontinence (SUI): ODE Clinical Review

Julia Carey-Corrado, MD

Obstetrics and Gynecology Devices Branch
Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation (ODE)
General Issue Device Panel

• Generic view of device category (suburethral mesh slings for SUI)
  – Custom features (e.g. needle passers, sleeves, tissue anchors, etc.) will not be discussed
Outline

• SUI: Public Health Perspective
• Non-pharmacologic therapies for female SUI
• Comparative safety and effectiveness outcomes on 1st generation minimally invasive mesh slings
  – Cochrane Collaboration Reviews
  – Richter et al. 2010 NEJM
• Preliminary findings and comparative data on 2nd generation mesh “mini-slings”
• Clinical summary
  – Premarket, postmarket (ODE viewpoint)
Prevalence of Female Urinary Incontinence

• 15.7%\(^1\)
  – All types of incontinence
  – Moderate to severe leakage

• Types of urinary incontinence\(^2\)
  – Stress urinary incontinence (SUI) 48%
  – Urge incontinence 17%
  – Mixed incontinence 34%

• 11% lifetime risk of surgery for prolapse or incontinence\(^3\)

\(^1\) 2005-2006 National Health and Nutrition Examination Survey (NHANES)
\(^2\) Nitti VW Rev Urology (2001)
\(^3\) Olsen et al. Obstet Gynecol (1997)
Treatment Options for SUI

- Pelvic Floor Muscle Training
- Mechanical Support Devices
- Transurethral Bulking Agents
- Transurethral RF Tissue Remodeling
- Surgery (bladder neck and mid-urethral support)
Bladder Neck and Suburethral Support Surgery

More Invasive
- Open retropubic colposuspension
- Pubovaginal sling*
- Bladder neck needle suspension

Minimally Invasive – Use Mesh
- (1st generation) suburethral mesh sling
- (2nd generation) single-incision mini-sling
* May use mesh
Surgical Procedures for SUI (2010)

Invasive and Minimally Invasive

- Invasive (Non-Mesh)
  - 54,000 (21%)

- Minimally Invasive (Mesh)
  - 206,000 (79%)

*Midurethral Slings*

*Industry Source*
1st Generation
Minimally-Invasive Suburethral Slings

• Provide mechanical support for urethra

Retropubic
– bottom-to-top
– top-to-bottom

Transobturator
– medial-to-lateral
– lateral-to-medial

Images courtesy of C.R. Bard
FDA Clinical Review: Cochrane Collaboration Systematic Reviews

• Cochrane Collaboration
  – Prospective RCTs (Quality Level I evidence)*
  – (At least) one study arm randomized to mesh
  – Comparative data for all outcomes evaluated
  – Meta-analytic technique for pooling multiple data sets

* US Preventive Services Task Force
FDA Clinical Review: Cochrane Collaboration Meta-Analysis

- Definition of “cure/failure” not uniform across studies
- Uneven weighting of studies
- Possible bias (e.g. unmasked treatment arm)
- No subgroup analyses for
  - Symptoms
  - Diagnosis
  - Prior failed surgery
  - Single or multiple procedure (e.g. prolapse)
  - Surgeon experience
1st Generation Mesh Slings: Cochrane Comparative Effectiveness Outcomes

- Colposuspension vs. 1st Generation Mesh Sling\(^4\)
  - Cochrane Meta-Analysis
  - Ward KL et al. 6-month, 2- and 5-year outcomes

- Mesh Sling vs. Mesh Sling\(^5\)
  - Retropubic vs. Transobturator
  - (Retropubic bottom-to-top vs. top-to-bottom)
  - (Transobturator medial-to-lateral vs. lateral-to-medial)

## Comparative Effectiveness of Colposuspension vs. 1st Generation Mesh Slings

<table>
<thead>
<tr>
<th></th>
<th>Open Colposuspension</th>
<th>1st Generation Mesh Sling</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Year Failure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjective</td>
<td>26%</td>
<td>31%</td>
<td>0.85 (0.63, 1.17)</td>
</tr>
<tr>
<td>(3 studies; N=400)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective</td>
<td>19%</td>
<td>19%</td>
<td>1.02 (0.67, 1.56)</td>
</tr>
<tr>
<td>(2 studies; N=368)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Comparative Effectiveness of Colposuspension vs. 1st Generation (Retropubic) Mesh Slings

<table>
<thead>
<tr>
<th>1-5 Year Failure</th>
<th>Open Colposuspension</th>
<th>1st Generation Mesh Sling</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective</td>
<td>29%</td>
<td>32%</td>
<td>0.92 (0.67, 1.26)</td>
</tr>
<tr>
<td>Objective</td>
<td>17%</td>
<td>14%</td>
<td>1.22 (0.72, 2.06)</td>
</tr>
</tbody>
</table>

29% 32% 0.92 (0.67, 1.26)

## Comparative Effectiveness of Colposuspension vs. 1st Generation (Retropubic) Mesh Slings⁴a

<table>
<thead>
<tr>
<th></th>
<th>Open Colposuspension (N=169)</th>
<th>1st Generation Mesh Sling (N=175)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6-Month Cure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjective*</td>
<td>71%</td>
<td>66%</td>
<td>0.95</td>
</tr>
<tr>
<td>Objective†</td>
<td>57%</td>
<td>66%</td>
<td>0.099</td>
</tr>
</tbody>
</table>

* Bristol Female Lower Urinary Tract Symptoms Questionnaire (e.g. any symptom of stress incontinence)

† Negative stress test on urodynamic testing + negative 1-hour pad test (< 1g change weight)

Comparative Effectiveness of Colposuspension vs. 1<sup>st</sup> Generation (Retropubic) Mesh Slings<sup>4b</sup>

<table>
<thead>
<tr>
<th></th>
<th>Open Colposuspension (N=169)</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Generation Mesh Sling (N=175)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Year Cure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjective*</td>
<td>78%</td>
<td>79%</td>
<td>0.26</td>
</tr>
<tr>
<td>Objective† (ITT; withdrawals failures)</td>
<td>51%</td>
<td>63%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Bristol Female Lower Urinary Tract Symptoms Questionnaire (e.g. any symptom of stress incontinence)

† Negative stress test on urodynamic testing + negative 1-hour pad test (< 1g change weight)

Comparative Effectiveness of Colposuspension vs. 1st Generation (Retropubic) Mesh Slings\textsuperscript{4c}

<table>
<thead>
<tr>
<th>5 Year Cure</th>
<th>Open Colposuspension (N=49)</th>
<th>1\textsuperscript{st} Generation Mesh Sling (N=72)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective*</td>
<td>76%</td>
<td>71%</td>
<td>0.54</td>
</tr>
<tr>
<td>Objective+ (Evaluable Patients)</td>
<td>90%</td>
<td>81%</td>
<td>0.21</td>
</tr>
</tbody>
</table>

\* Bristol Female Lower Urinary Tract Symptoms Questionnaire (e.g. any symptom of \textit{stress incontinence})

\+ Negative 1-hour pad test (< 1g change weight)

\textsuperscript{4c} Ward KL \textit{et al}. BJOG (2007)
Comparative Effectiveness of 1\textsuperscript{st} Generation Mesh Slings (Mesh vs. Mesh)\textsuperscript{5}

<table>
<thead>
<tr>
<th></th>
<th>Transobturator</th>
<th>Retropubic</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Year Cure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjective (10 studies; N=1281)</td>
<td>85%</td>
<td>84%</td>
<td>1.00 (0.96, 1.05)</td>
</tr>
<tr>
<td>Objective (17 studies; N=2434)</td>
<td>84%</td>
<td>88%</td>
<td>0.96 (0.93, 0.99)</td>
</tr>
</tbody>
</table>

\textsuperscript{5} Ogah J \textit{et al.}. Cochrane Database Sys Rev (2010)
## Comparative Effectiveness of 1\textsuperscript{st} Generation Mesh Slings (Mesh vs. Mesh)

<table>
<thead>
<tr>
<th>1 Year Cure</th>
<th>Transobturator (N=292)</th>
<th>Retropubic (N=291)</th>
<th>% Point Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective*</td>
<td>56%</td>
<td>62%</td>
<td>6% (-1.6, 14.3)</td>
</tr>
<tr>
<td>Objective(\dagger) (Per Protocol)</td>
<td>78%</td>
<td>81%</td>
<td>3% (-3.6, 9.6)</td>
</tr>
</tbody>
</table>

* No self reported symptoms (Medical, Epidemiological and Social Aspects of Aging (MESA) Questionnaire; no leak 3-day diary)

\(\dagger\) Negative provocative stress test + negative 24-hour pad test + no retreatment

\(6\) Richter HE \textit{et al.} NEJM (2010)
1\textsuperscript{st} Generation Mesh Slings: Comparative Safety Outcomes

- Colposuspension vs. 1\textsuperscript{st} Generation Mesh Slings
- Mesh Sling v. Mesh Sling
  - Transobturator vs. Retropubic
  - (Retropubic bottom-to-top vs. top-to-bottom)
  - (Transobturator medial-to-lateral vs. lateral-to-medial)
## Comparative Safety of Colposuspension vs. 1st Generation Slings (at 6-12 months)\(^4\)

<table>
<thead>
<tr>
<th></th>
<th>Open Colposuspension (N=146)</th>
<th>1st Generation Mesh Sling (N=196)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peri-operative Surgical Complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder Injury (2 studies; N=121)</td>
<td>2%</td>
<td>9%</td>
<td>P-value 0.013 (0.28, 2.61)</td>
</tr>
<tr>
<td>Bladder Perforation</td>
<td>1%</td>
<td>7.1%</td>
<td>0.19 (0.07, 0.52)</td>
</tr>
<tr>
<td>Vascular Injury (5 studies; N=653)</td>
<td>0%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Voiding Difficulty (4 studies; N=501)</td>
<td>5.4%</td>
<td>5.7%</td>
<td>0.92 (0.46, 1.85)</td>
</tr>
<tr>
<td>Mesh Erosion (1 study; N=316)</td>
<td>NA</td>
<td>1%</td>
<td>1.94 (0.47, 7.98)</td>
</tr>
<tr>
<td>Repeat Incontinence Surgery</td>
<td>3.4%</td>
<td>1.8%</td>
<td></td>
</tr>
</tbody>
</table>


Comparative Safety of Colposuspension vs. 1\textsuperscript{st} Generation Slings (at 6 months)\textsuperscript{4a}

<table>
<thead>
<tr>
<th></th>
<th>Open Colposuspension (N=146)</th>
<th>1\textsuperscript{st} Generation Mesh Sling (N=170)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder Injury</td>
<td>2%</td>
<td>9%</td>
<td>0.013</td>
</tr>
<tr>
<td>Vascular Injury</td>
<td>0%</td>
<td>1%</td>
<td>1.0</td>
</tr>
<tr>
<td>Mesh Erosion</td>
<td>NA</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{4a} Ward KL \textit{et al.} BMJ (2002)
### Comparative Safety of Colposuspension vs. 1st Generation Slings (at 5 years)\(^{4c}\)

<table>
<thead>
<tr>
<th></th>
<th>Open Colposuspension</th>
<th>1st Generation Mesh Sling</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mesh Erosion</strong></td>
<td>NA</td>
<td>3.5%</td>
<td></td>
</tr>
<tr>
<td><strong>Prolapse Surgery</strong></td>
<td>7.5%</td>
<td>1.8%</td>
<td>0.025</td>
</tr>
<tr>
<td><strong>Repeat Incontinence Surgery</strong></td>
<td>3.4%</td>
<td>2.3%</td>
<td>0.74</td>
</tr>
</tbody>
</table>

\(^{4c}\) Ward KL et al. BJOG (2007)
# Comparative Safety of 1st Generation Mesh Slings

<table>
<thead>
<tr>
<th>Condition</th>
<th>Transobturator</th>
<th>Retropubic</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder/Urethral Perforation</td>
<td>0.3%</td>
<td>5.5%</td>
<td>0.14 (0.07, 0.26)</td>
</tr>
<tr>
<td>(18 studies; N=2674)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-Op Voiding Difficulty</td>
<td>4.3%</td>
<td>7.1%</td>
<td>0.63 (0.44, 0.89)</td>
</tr>
<tr>
<td>(14 studies; N=2085)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal Mesh Erosion</td>
<td>2.1%</td>
<td>1.3%</td>
<td>1.58 (0.83, 3.00)</td>
</tr>
<tr>
<td>(14 studies; N=2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Groin pain/retropubic pain</td>
<td>12.0%</td>
<td>1.5%</td>
<td>5.95 (3.22, 11.02)</td>
</tr>
<tr>
<td>(8 studies; N=1050)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat Incontinence Surgery</td>
<td>7.6%</td>
<td>5.1%</td>
<td>1.52 (0.90, 2.59)</td>
</tr>
<tr>
<td>(5 studies; N=746)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Comparative Safety 1st Generation Mesh Slings

<table>
<thead>
<tr>
<th></th>
<th>Transobturator (N=299)</th>
<th>Retropubic (N=298)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Any Serious Adverse Event (SAE)</td>
<td>6.4%</td>
<td>13.8%</td>
<td>0.003</td>
</tr>
<tr>
<td>Wound-Related SAE (includes mesh erosion)</td>
<td>1.7%</td>
<td>3%</td>
<td>0.30</td>
</tr>
<tr>
<td>Genitourinary SAE</td>
<td>4.3%</td>
<td>7.7%</td>
<td>0.09</td>
</tr>
<tr>
<td>Voiding Dysfunction</td>
<td>0%</td>
<td>2.7%</td>
<td>0.004</td>
</tr>
</tbody>
</table>

---

6 Richter HE et al. NEJM (2010)
Clinical Conclusions: 1st Generation Mesh Slings

Effectiveness
• 1st generation minimally-invasive mesh slings as effective as open colposuspension
• Large body of comparative outcomes data for mesh vs. mesh demonstrates effectiveness
  – Cure/failure rates ~consistent across studies
  – Limited data beyond 1 year

Safety
• Vaginal mesh erosion up to 3.5%
  – Vaginal erosion from SUI mesh (3.5%) lower compared to POP mesh (10%)
• Retropubic v. Transobturator trade-off
  – ↑ Risk of bladder injury
  – ↑ Risk of voiding dysfunction
  – ↓ Risk of groin pain

*Average overall incidence reported as 6% in Stanford EJ et al J Min Invas Gynecol (2008)
2nd Generation Slings: Single-Incision Mini-Slings

- Goal to decrease risk of:
  - groin pain
  - bladder perforation
Effectiveness of 2\textsuperscript{nd} Generation Mesh Sling: Meta-Analysis of 12-month Outcomes\textsuperscript{7}

- Subjective Cure 76\% (8 studies; N=1024)
- Objective Cure 76\% (6 studies; N=683)

\textsuperscript{7} Walsh CA BJU Internat (2011)
Safety of 2\textsuperscript{nd} Generation Mesh Sling: Meta-Analysis of 12-month Outcomes\textsuperscript{7}

- Complications
  - Vaginal Mesh Exposure 2.4\% (10 studies; N=1178)
  - Recurrent SUI 5\% (5 studies; N=799)
  - De Novo Overactive Bladder 10\% (8 studies; N=832)

\textsuperscript{7} Walsh CA BJU Internat (2011)
Comparative Effectiveness of 1\textsuperscript{st} Generation Mesh Sling vs. 2\textsuperscript{nd} Generation Mesh Mini-Sling\textsuperscript{8}

<table>
<thead>
<tr>
<th></th>
<th>1\textsuperscript{st} Generation Mesh Sling (N=38)</th>
<th>2\textsuperscript{nd} Generation Mesh Sling (Mini-Sling) (N=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Year Cure* (Objective)</td>
<td>81.6%</td>
<td>83.8%</td>
</tr>
</tbody>
</table>

\textsuperscript{8} Tommaselli GA \textit{et al.} Int Urogyn J (2010)

Cough stress test; urodynamic evaluation
## Comparative Effectiveness of 1st Generation Mesh Sling vs. 2nd Generation Mesh Mini-Sling

<table>
<thead>
<tr>
<th></th>
<th>1st Generation Mesh Sling (N=92)</th>
<th>2nd Generation Mesh Sling (Mini-Sling) (N=96)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Year Failure</strong></td>
<td>Objective*</td>
<td>2.4%</td>
<td>16.4%</td>
</tr>
<tr>
<td></td>
<td>Subjective†</td>
<td>8.3%</td>
<td>24.0%</td>
</tr>
</tbody>
</table>

* Standing cough stress test w/bladder volume 300cc or >70% max capacity
† Any incontinence episode during previous month

---

Comparative Safety of 1\textsuperscript{st} Generation Mesh Sling vs. 2\textsuperscript{nd} Generation Mesh Mini-Sling\textsuperscript{8}

<table>
<thead>
<tr>
<th></th>
<th>1\textsuperscript{st} Generation Mesh Sling (N=38)</th>
<th>2\textsuperscript{nd} Generation Mesh Sling (Mini-Sling) (N=37)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Retention</td>
<td>5.2% (2/38)</td>
<td>0% (0/37)</td>
<td>0.49</td>
</tr>
<tr>
<td>Vaginal Erosion</td>
<td>0% (0/38)</td>
<td>2.7% (1/37)</td>
<td>0.49</td>
</tr>
<tr>
<td>Leg Pain</td>
<td>7.9% (3/38)</td>
<td>0% (0/37)</td>
<td>0.24</td>
</tr>
<tr>
<td>De Novo Urgency</td>
<td>2.6% (1/38)</td>
<td>5.4% (2/37)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

\textsuperscript{8} Tommaselli GA \textit{et al.} Int Urogyn J (2010)
Comparative Safety of 1\textsuperscript{st} Generation Mesh Sling vs. 2\textsuperscript{nd} Generation Mesh Mini-Sling\textsuperscript{9}

<table>
<thead>
<tr>
<th></th>
<th>1\textsuperscript{st} Generation Mesh Sling (N=92)</th>
<th>2\textsuperscript{nd} Generation Mesh Sling (Mini-Sling) (N=96)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal Mesh Erosion</td>
<td>1%</td>
<td>7%</td>
<td>7.6 (0.8, 74.0)</td>
</tr>
<tr>
<td>Reoperation for SUI within 12 months</td>
<td>0%</td>
<td>15%</td>
<td>2.3 (1.9, 2.7)</td>
</tr>
</tbody>
</table>

\textsuperscript{9} Hinoul P \textit{et al.} J Urol (2011)
Clinical Conclusions:
2nd Generation Mesh Slings

Effectiveness
- Possibly less effective at 12 months compared to 1st generation mesh slings
  - Meta-analysis dominated by non-randomized studies
  - Limited prospective comparative outcomes data
  - Possible “learning curve” bias

Safety
- Similar types of risks as 1st generation mesh
  - Too early to quantitate level of risk
ODE Clinical Conclusions

• Premarket Review: New SUI Mesh Slings
  – No premarket data for 1st Generation Slings
  – Premarket data for 2nd Generation Mini-Slings
    • Class II comparison to 1st Generation Sling

• Post-Market Review: FDA cleared, legally marketed
  – No postmarket data for 1st Generation Slings
  – Postmarket data for 2nd Generation Mini-Slings
Surgical Mesh for SUI

Recap and Panel Questions

Jill Brown, MD/MPH, FACOG
CDR USPHS
Office of Device Evaluation
Key Messages

• Safety
  – persistent MDR signal
  – serious adverse events reported in literature
  – erosion < 5%

• Effectiveness
  – 1\textsuperscript{st} generation slings as effective as non-mesh surgery; clinically accepted standard of care

• Limited data on mini-slings
Concerns with SUI Data

- Question whether existing data affords sufficient understanding of risks for all serious AEs
- Heterogeneous outcome measures may limit comparability across studies
- Majority of data 1-year follow-up
- Indication of lower success rates and higher complication rates for mini-slings
Regulatory Conclusions

- Pre-market: clinical data needed for new mini-slings (not 1st generation slings)
  - can compare to 1st generation slings
  - 510(k) still appropriate for SUI indication
  - up-classification to Class III not necessary

- Post-market: different viewpoints
  - Post-market studies needed for entire class vs.
  - Post-market studies only needed for mini-slings
Viewpoints on SUI Data

• One view
  – existing data does not afford sufficient understanding of risks for all serious AEs
  – postmarket data needed for entire class

• Other view
  – risks for 1st generation devices adequately characterized in existing literature
  – postmarket data only needed for mini-slings

• Asking Panel to weigh in on these questions
Thank you!

Questions?
Panel Questions
Question 1 Part a: 
Effectiveness of surgical mesh for SUI repair

Considering the available evidence, is there reasonable assurance that first-generation minimally invasive suburethral slings for SUI repair are effective?
Question 1 Part b: Safety of surgical mesh for SUI repair

• Is the list of risks prepared by FDA complete and accurate?

• Given the available evidence on incidence and severity of these adverse events, is there reasonable assurance of safety?
Question 1 Part c

*Surgical mesh for SUI repair*

Considering the available evidence, do the benefits outweigh the risks?
Question 1 Part d
Surgical mesh for SUI repair

• Are clinical studies needed before FDA clears/approves new surgical mesh products for SUI repair?

• If yes, what type(s) of clinical studies?
  • Consider patient selection/exclusion (e.g., concomitant surgeries), outcome measures, follow-up duration, and controls.
Question 1 Part e
Surgical Mesh for SUI Repair: Postmarket Studies

• Are postmarket studies needed for currently marketed surgical mesh products for SUI repair?

• If so, what type(s) of studies are needed?
Question 2 Part a

Single incision mini-slings

Based on the available scientific evidence, is there adequate safety and effectiveness data to support the use of single-incision mini-slings?
Question 2 Part b

*Single incision mini-slings*

- Are clinical studies needed before FDA clears/approves new single incision mini-slings?

- If yes, what type(s) of clinical studies?

  - Consider patient selection/exclusion (e.g., concomitant surgeries), outcome measures, follow-up duration, and controls.
Question 2 Part c

Single incision mini-slings: Postmarket Studies

• Are postmarket studies needed for currently marketed single incision mini-slings?

• If so, what type(s) of studies are needed?

• Consider patient selection/exclusion (e.g., concomitant surgeries), outcome measures, follow-up duration, and controls.
Thank You