Update on Surgical Mesh for Pelvic Organ Prolapse (POP)

FDA Meeting of the Obstetric and Gynecologic Devices Panel

September 8, 2011
Introduction

Jeff Secunda
Vice-President, Technology & Regulatory Affairs
AdvaMed
Presentation Objectives

- Transvaginal mesh is safe and effective for treating POP
- Can be appropriately regulated within Class II and 510(k) clearance paradigm
- Current regulatory pathway fostered development and continued improvement
<table>
<thead>
<tr>
<th>Agenda</th>
<th>Suzette E. Sutherland, MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmet Medical Need</td>
<td>Surgeon, Metro Urology</td>
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<tr>
<td></td>
<td>Adjunct Associate Professor</td>
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<td></td>
<td>University of Minnesota</td>
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<tr>
<td>Clinical Overview</td>
<td>Piet Hinoul, MD, PhD</td>
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<td></td>
<td>Director, Medical Affairs</td>
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<td>Ethicon Women’s Health and Urology</td>
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<td>Regulatory Pathways</td>
<td>Ginger Glaser</td>
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<td>Sr. Director, Global Quality &amp; Regulatory Affairs</td>
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<td>American Medical Systems</td>
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</tbody>
</table>
Clinical Experience of Transvaginal Mesh for Pelvic Organ Prolapse

Suzette E. Sutherland, MD
Important Treatment Option

- Mischaracterizing benefit/risk profile
- Complex surgery
- Serious complications are very rare
- Mesh procedures provide a lasting benefit
Pelvic Organ Prolapse (POP)

Normal female pelvic anatomy

Urethrocele with moderate cystocele

Uterine prolapse

Vaginal vault prolapse

Enterocoele

Rectocoele
Complicated Condition
Different Treatment Options

- Colporrhaphy
  - Native tissue repair
  - With apical repair
    - USL or SSL

- Abdominal sacral colpopexy
  - Includes synthetic mesh
  - Open, Lap or Robotic

- Transvaginal mesh
  - Includes synthetic mesh
Counseling Considerations

- Type of prolapse
- Severity
- Prior surgeries (especially prolapse)
- Concomitant pelvic symptoms
- Medical co-morbidities
- Age
- Sexual activity
Surgical Mesh Procedures Began with Flat Mesh Grafts

Mansoor

Migliari

Eglin

Nicita
Transvaginal Mesh Kits 
Advanced the Procedure

- Made procedures more consistent
- Helped surgeons to operate in harder-to-reach parts of vagina
- Less invasive vs. abdominal approach
- Standardized tools help surgeons
Mesh Literature

- Anatomic superiority seen with mesh
- Mesh vs. Non-mesh QoL improvements equivalent
- Follow-up 1 year: not sufficient
- Anatomic superiority predicts future outcomes
Outcomes Are Related to Experience

- Experience of surgeon is critical
- Must understand differences in procedures: mesh vs. no mesh
- Increased surgical experience helps reduce complications
Vaginal Mesh Exposure

- Usually occur in the first year
  - Associated with initial wound healing

- Minor and easily managed
  - Topical estrogen application
  - Minor surgical excision and repair
Mesh Erosion

- Very rare
  - Most associated with interoperative malplacement

- Manageable in experienced surgical hands
  - Transvaginally or endoscopically
De Novo Dyspareunia

- Complications can arise from
  - Tensioning/bunching
  - Narrowing of vaginal canal

- Treatments
  - Vaginal/pelvic floor PT
  - Releasing incisions in the mesh
Risks with All Surgical Options

COLPORRAPHY

SACRAL COLPOPEXY
Conclusions
Transvaginal Mesh

- Important treatment option for women
- Surgery is complex; should only be done by experienced surgeon
- Continuing medical advances for this condition is critical
Safety & Efficacy

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

- Address FDA questions
- Discuss data regarding benefit-risk profile
- Outline clinical proposals for transvaginal mesh
Pre-Clinical and Clinical Studies

- Numerous 1-3 year studies
- 5-year studies in progress
- Bench and *in vivo* testing
  - Biocompatibility
  - Biomechanics
  - Animal studies
  - Anatomical models
  - Computer models
Complicated Disease with Several Surgical Options

- Transvaginal Mesh
- Abdominal Sacrocolpopexy

Patient’s General Condition

- Middle Compartment
- Anterior Compartment
- Posterior Compartment

Native Tissue Repair
Pelvic Organ Prolapse Treatment Algorithm

Patient

Labeling

Surgeon

Benefit/Risk Profile

Informed Decision
Effectiveness of Transvaginal Mesh

- Significant higher anatomic cure rate vs. traditional surgeries
- Significant improvement in QoL measures comparable to traditional surgeries
Anatomic Cure Rate is the Most Objective Clinical Measure

- POP-Q Score
  - ICS, 1995
  - AUGS, 1996
  - SGS, 1996
  - NIH, 2001

- FDA proposes anatomy as a co-primary endpoint
**RCTs Demonstrate Anatomic Superiority of Transvaginal Mesh**

<table>
<thead>
<tr>
<th>RCT</th>
<th>N</th>
<th>Follow-up (months)</th>
<th>Anatomic Cure</th>
<th>p</th>
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<tbody>
<tr>
<td>Sivaslioglu (2008)</td>
<td>90</td>
<td>12</td>
<td>91% Ant 72%</td>
<td>p&lt;0.05</td>
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<td>Nguyen (2008)</td>
<td>75</td>
<td>12</td>
<td>87% Ant 55%</td>
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<td>Carey (2009)</td>
<td>139</td>
<td>12</td>
<td>81% Ant 65.6%</td>
<td>p=0.07</td>
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<tr>
<td>Nieminen (2010)</td>
<td>202</td>
<td>36</td>
<td>87% Ant 59%</td>
<td>p&lt;0.0001</td>
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<tr>
<td>Iglesia (2010)</td>
<td>65</td>
<td>9.7</td>
<td>40.6 All 29.6</td>
<td>p=0.28</td>
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<tr>
<td>Withagen (2011)</td>
<td>194</td>
<td>12</td>
<td>90.4 All 54.8</td>
<td>p&lt;0.001</td>
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<tr>
<td>Altman (2011)</td>
<td>389</td>
<td>12</td>
<td>82.3 Ant 47.5</td>
<td>p=0.008</td>
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</tbody>
</table>
### RCTs Demonstrate Improvement of QoL Measures of Transvaginal Mesh

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Follow-up (months)</th>
<th>Functional Outcome</th>
<th>Mesh</th>
<th>Traditional</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Nieminen (2010)</td>
<td>202</td>
<td>36</td>
<td>‘all symptoms’</td>
<td>‘all symptoms’</td>
<td>Pre: 100% Post: 28%</td>
<td>NS</td>
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<tr>
<td>Iglesia (2010)</td>
<td>65</td>
<td>3</td>
<td>PFDI-20</td>
<td>PFDI-20</td>
<td>Pre:100 Post:42.9</td>
<td>NS</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PFIQ-7</td>
<td>PFIQ-7</td>
<td>Pre:23.8 Post:4.8</td>
<td>NS</td>
</tr>
<tr>
<td>Withagen (2011)</td>
<td>194</td>
<td>12</td>
<td>UDI Prolapse</td>
<td>UDI Prolapse</td>
<td>Pre:48 Post:5</td>
<td>NS</td>
</tr>
<tr>
<td>Altman (2011)</td>
<td>389</td>
<td>12</td>
<td>UDI</td>
<td>UDI</td>
<td>Pre: 86.9 Post:53.6</td>
<td>NS</td>
</tr>
<tr>
<td>Carey (2009)</td>
<td>139</td>
<td>12</td>
<td>PSI-QoL mean change</td>
<td>PSI-QoL mean change</td>
<td>Pre- Post: -6.9 Pre- Post: -7.8</td>
<td>NS</td>
</tr>
</tbody>
</table>
### NEJM Study Demonstrates Higher Cure Rate for Transvaginal Mesh

**Outcome Measure** (at 1 year) | **Colphorrhaphy**<br>n=189 | **Mesh Repair**<br>n=200 | **p-value**
---|---|---|---
Cure Rate | 47.5% | 82.3% | <0.001
No Vaginal Bulge Symptom | 62.1% | 75.4% | 0.008
Successful Composite Primary Outcome | 34.5% | 60.8% | <0.001

Altman NEJM, 2011
Safety of Transvaginal Mesh

- Serious adverse event rate is low
- Serious mesh-specific adverse event rate is very low
- Adverse event rate is comparable to traditional surgery
- Mesh-specific adverse events are manageable
“MAUDE data is not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices.”
Exposure ≠ Erosion

- Mesh exposure – mesh exposed in the vagina
- Mesh erosion – perforation into a hollow organ
Management of Exposure

- 110 studies – 11,785 women

- Exposure rate: 10.3%
  - Treatment of exposure
    - 11% no treatment
    - 21% topical estrogen
    - 11% in-office procedure
    - 56% partial surgical excision

Abed et al. 2011
Risk Factors for Mesh Exposure

- Hysterectomy
- Patients’ Increasing Age
- Smoking
- Diabetes
- Surgeon Experience
  - Exposure rates: 2.9% (Experienced surgeon) vs. 15.6% (Fellow)
  - Years of experience in prolapse repair, not mesh procedures, appeared to be protective

Abed et al. 2011; Achtari, et al. 2005; Withagen et al. 2011
## Complication Rates in Perspective: Dyspareunia

<table>
<thead>
<tr>
<th>Dyspareunia</th>
<th>Sacrocolpopexy</th>
<th>SSLF</th>
<th>USS</th>
<th>Colporrhaphy</th>
<th>Prolift</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>41%</td>
<td>-</td>
<td>21%</td>
<td>8%</td>
<td>37%</td>
</tr>
<tr>
<td><strong>De Novo</strong></td>
<td>15%</td>
<td>36%</td>
<td>26%</td>
<td>19%</td>
<td>17%</td>
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</table>

Lowman, AJOG, 2008
## Adverse Events in Literature

<table>
<thead>
<tr>
<th></th>
<th>Traditional Repair</th>
<th>Sacral Colpopexy</th>
<th>Mesh Kits</th>
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<tbody>
<tr>
<td>Number of studies</td>
<td>48</td>
<td>52</td>
<td>24</td>
</tr>
<tr>
<td>Subjects</td>
<td>7,827</td>
<td>5,639</td>
<td>3,425</td>
</tr>
<tr>
<td>Mesh exposure/ infection</td>
<td>0.5</td>
<td>2.2</td>
<td>5.8</td>
</tr>
<tr>
<td>Cystotomy</td>
<td>0.4</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Ureteral injury</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Bowel injury</td>
<td>0.4</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Bleeding complication</td>
<td>2.8</td>
<td>1.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Wound complications</td>
<td>0.5</td>
<td>1.5</td>
<td>0.2</td>
</tr>
<tr>
<td>PE / DVT</td>
<td>0.1</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Total reoperation rate</td>
<td>5.8</td>
<td>7.1</td>
<td>8.5</td>
</tr>
<tr>
<td>Total complication rate</td>
<td><strong>15.3</strong></td>
<td><strong>17.1</strong></td>
<td><strong>14.5</strong></td>
</tr>
</tbody>
</table>

Diwadkar G.Obs & Gyn, 2009
Benefit/Risk Profile

- Transvaginal mesh for the treatment of pelvic organ prolapse has a positive benefit/risk profile
- Published scientific literature show devices are
  - Effective
    - Anatomical restoration
    - Improvement in QoL measures
  - Safe
    - No new risks identified
    - Serious AEs remain low
- Important option for treatment of complicated disease
Clinical Studies for Pre-market Evaluation of Transvaginal Mesh

- Clinical data should continue to be generated for all new products
- Data should be included in the labeling
Key Considerations for Developing an Appropriate Clinical Plan

- Must be developed in conjunction with surgeons, manufacturers and FDA
- One trial design does not apply to all
- Study type dependent on specific question of safety and efficacy asked
Key Considerations for Developing an Appropriate Clinical Plan

- Indication for use
- Target patient population
- Performance expectation and key claims
- Pre-existing evidence
- Key questions to be addressed
Trial Design Considerations

- Multiple efficacy endpoints: Yes
- Non-inferiority design for low-incidence AEs: No
- RCT: When appropriate, Yes
  - Inherent Difficulties
    - Patient preference
    - Standardization of control arm
    - Difficulty blinding
Working Group Clinical Trial Proposal

- Single-arm prospective clinical trial
- Multiple endpoints
  - anatomy
  - symptoms
- Secondary endpoints could include
  - QoL measures
  - de novo dyspareunia
- Safety endpoints TBD
- Study duration
  - 1 year pre-approval
  - 3 - 5 years post-approval
Conclusion

- Superior in anatomic cure
- Comparable in QoL measures
- Serious adverse events (erosion) are very rare
- Adverse events (exposure) manageable
- Device manufacturers committed to
  - Collecting long-term data
  - Conducting pre-market clinical trials
Regulatory Pathway

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

- The regulatory controls necessary to provide reasonable assurance of safety and effectiveness of transvaginal POP mesh
Device Manufacturers/FDA Alignment

- Pre-market clinical trials for **new** products
- Additional post-market clinical data on current products
- Standardized labeling
  - Physician labeling presenting safety and effectiveness information based on clinical evidence
  - Patient labeling describing benefits and risks
- Pre-clinical studies specific to intended device use
- Device-specific physician training programs
Discussion Points

- Pre-market clinical trial design
- Device classification
Historical Perspective

- FDA surgical mesh guidance
- Post-market clinical trials
- Extensive physician training programs
Special Controls for Class II Devices

- Device specific pre-clinical testing
- Pre-market clinical studies
- Physician training
- Labeling requirements
  - Patient
  - Physician
- Post-market activities
  - Clinical studies, registries, surveillance
**Transvaginal Mesh for POP Repair Should Remain Class II**

<table>
<thead>
<tr>
<th>Submission Requirements</th>
<th>510(k)</th>
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<tbody>
<tr>
<td>Bench Data</td>
<td>✓</td>
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<tr>
<td>Pre-market Clinical Trials</td>
<td>✓</td>
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<tr>
<td>RCTs</td>
<td>✓</td>
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<tr>
<td>Physician Training</td>
<td>✓</td>
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<td>Patient and Physician Labeling Controls</td>
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<tr>
<td>Post-market Clinical Data</td>
<td>✓</td>
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<td>Active Surveillance</td>
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<tr>
<td>Design Control Detail</td>
<td>x</td>
</tr>
<tr>
<td>Manufacturing Controls and Inspection</td>
<td>x</td>
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</tbody>
</table>

- Clinical data presented in 510(k)s are intended **to establish equivalence** to a comparator of safety and efficacy.
- Clinical data presented in PMAs are intended **to establish** the standard of safety and efficacy.
Conclusion

- Transvaginal mesh is safe and effective
- Class II, 510(k) pathway is appropriate
Update on Surgical Mesh for Pelvic Organ Prolapse (POP)

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