

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

Agenda

Unmet Medical Need

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Clinical Overview

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Director, Medical Affairs
Ethicon Women's Health and Urology

Regulatory Pathways

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Clinical Experience of Transvaginal Mesh for Pelvic Organ Prolapse

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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

Anterior

Utero-vaginal / Superior

Posterior

Normal female pelvic anatomy

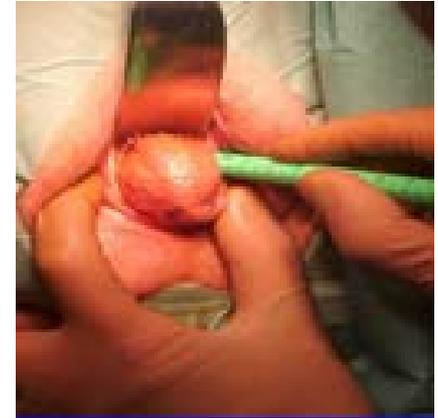
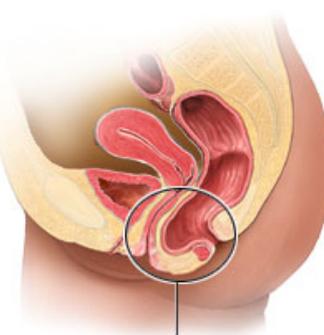
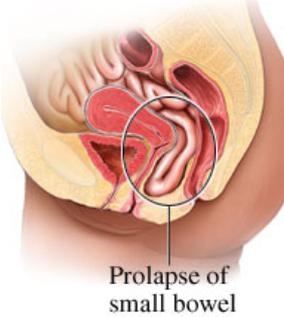
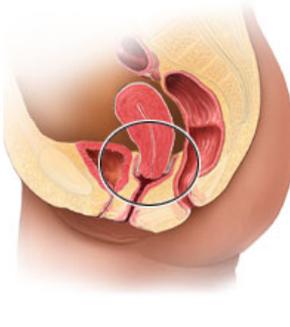
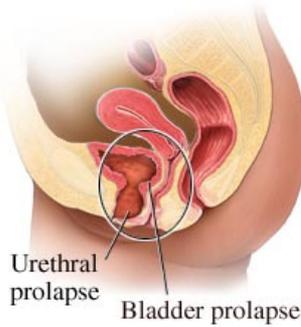
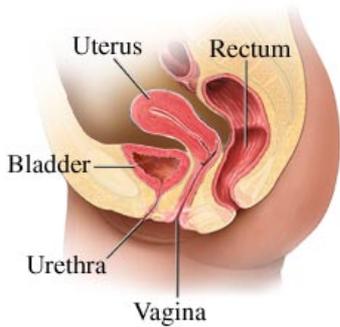
Urethrocele with moderate cystocele

Uterine prolapse

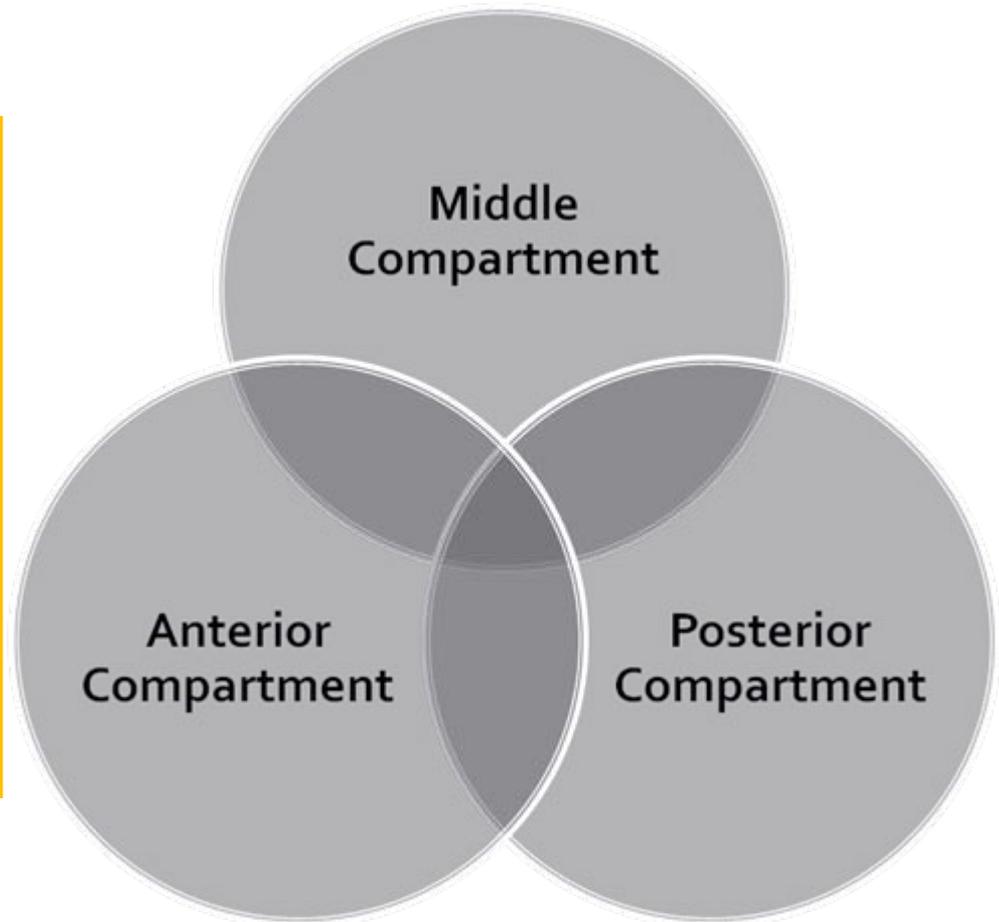
Vaginal vault prolapse

Enterocoele

Rectocele



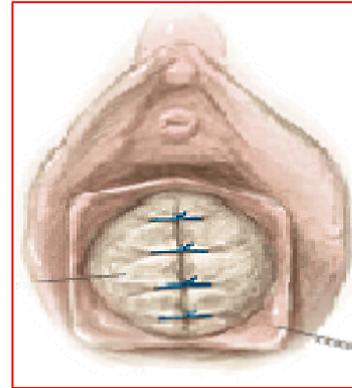
Complicated Condition



Different Treatment Options

- **Colporrhaphy**

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



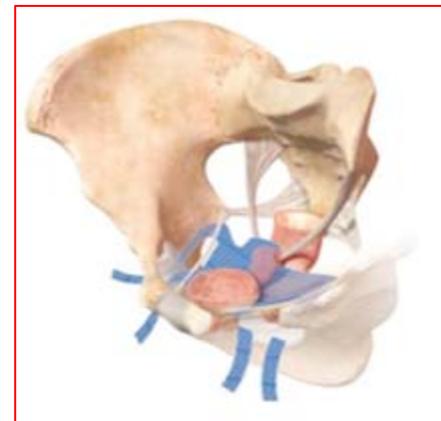
- **Abdominal sacral colpopexy**

- Includes synthetic mesh
- Open, Lap or Robotic



- **Transvaginal mesh**

- Includes synthetic mesh





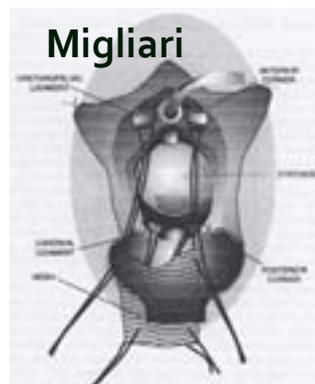
Counseling Considerations

- 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

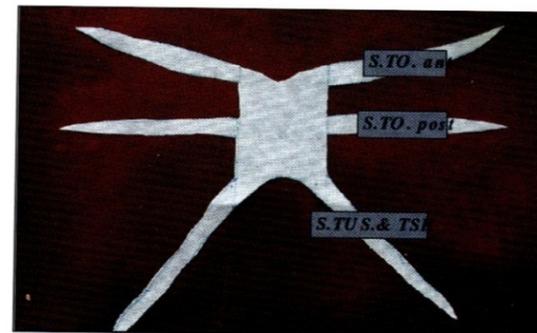
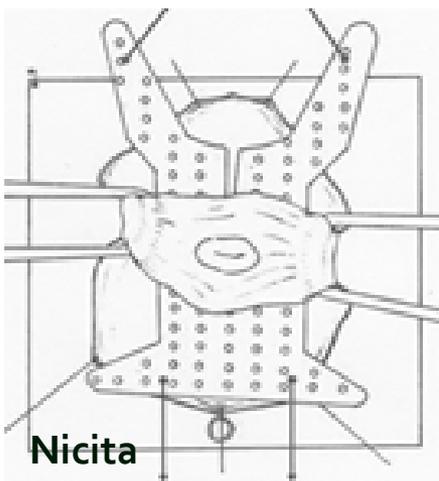


Photo 4. Prothèse : hamac vésical.

Eglin



Nicita

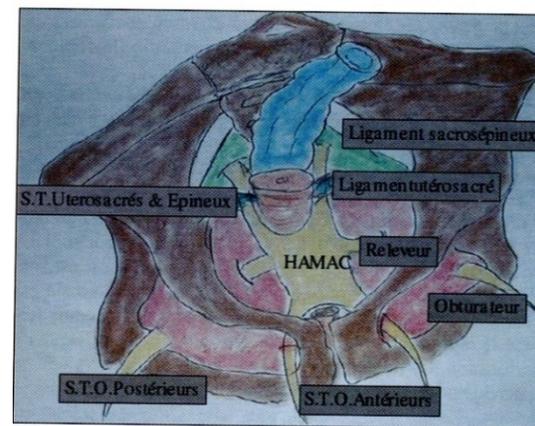
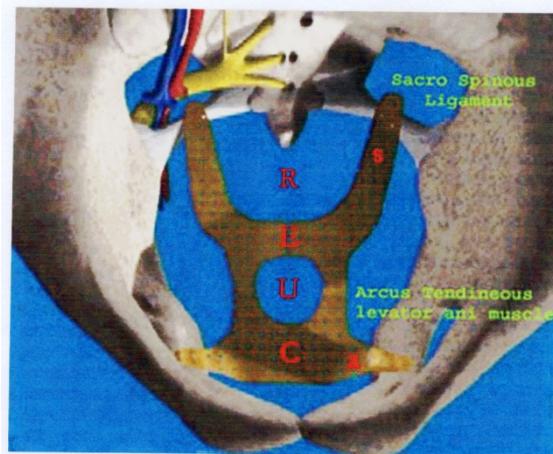


Photo 5. Hamac vesical.



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

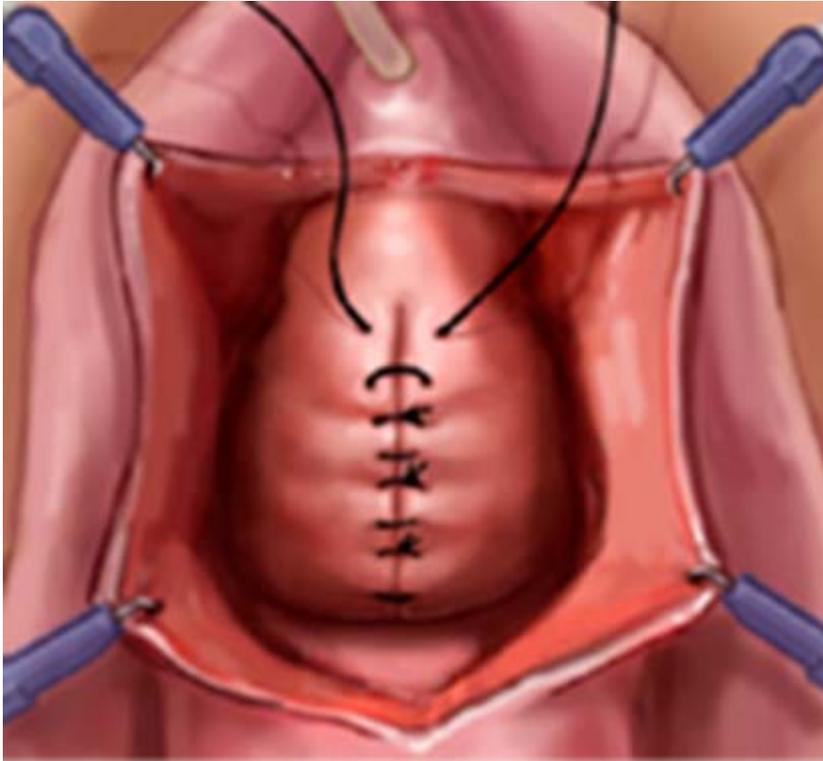


De Novo Dyspareunia

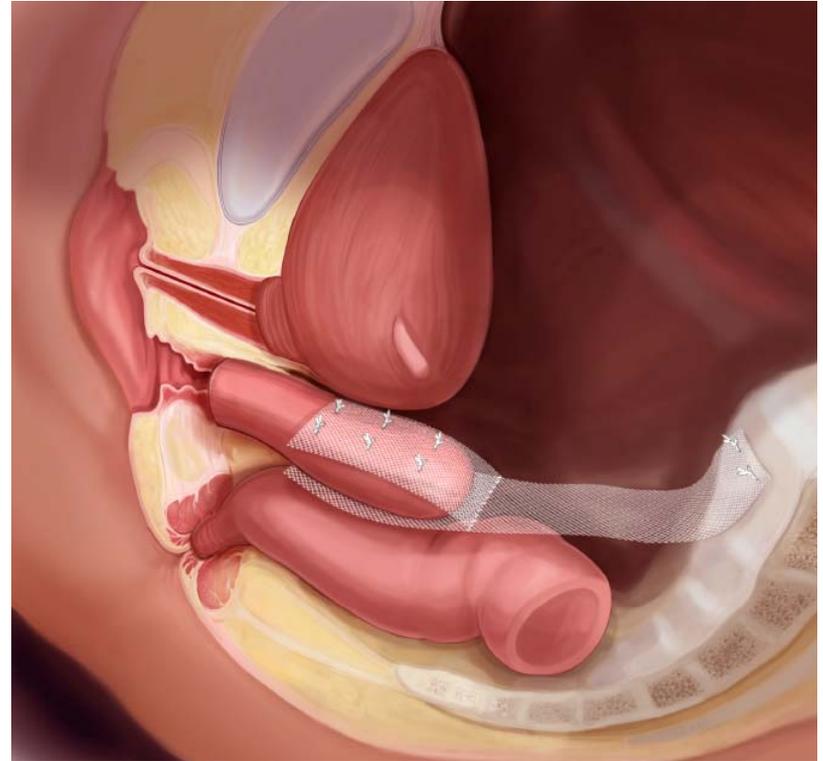
- Complications can arise from
 - Tensioning/bunching
 - Narrowing of vaginal canal
- Treatments
 - Vaginal/pelvic floor PT
 - Releasing incisions in the mesh

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

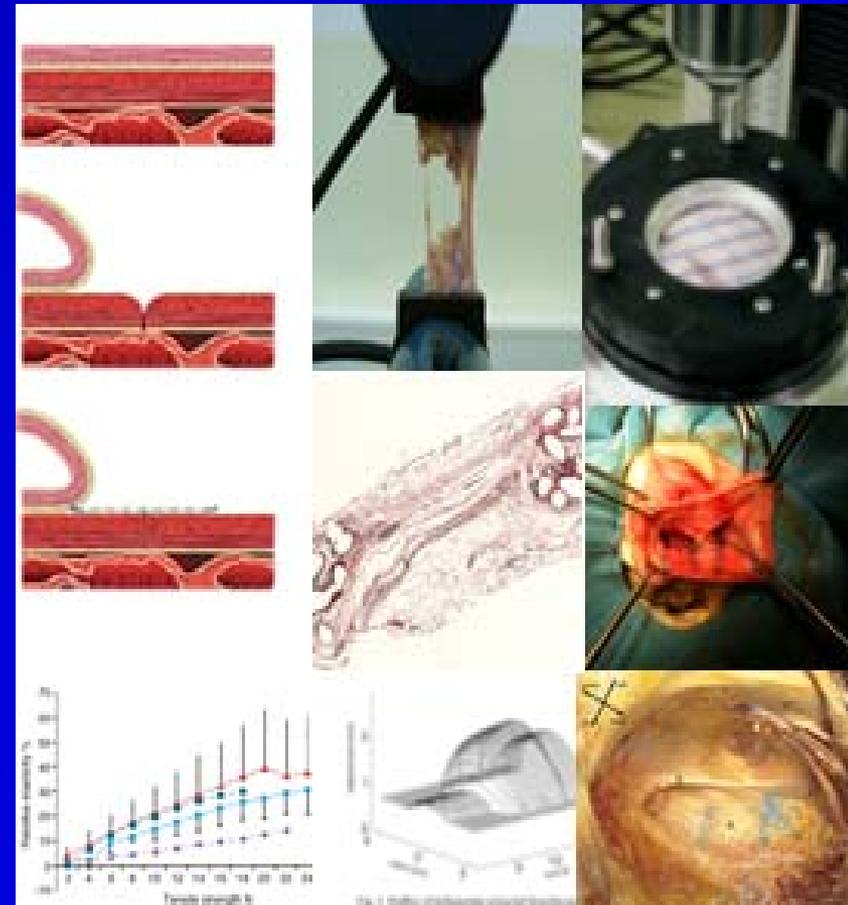
Ethicon Women's Health and Urology

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

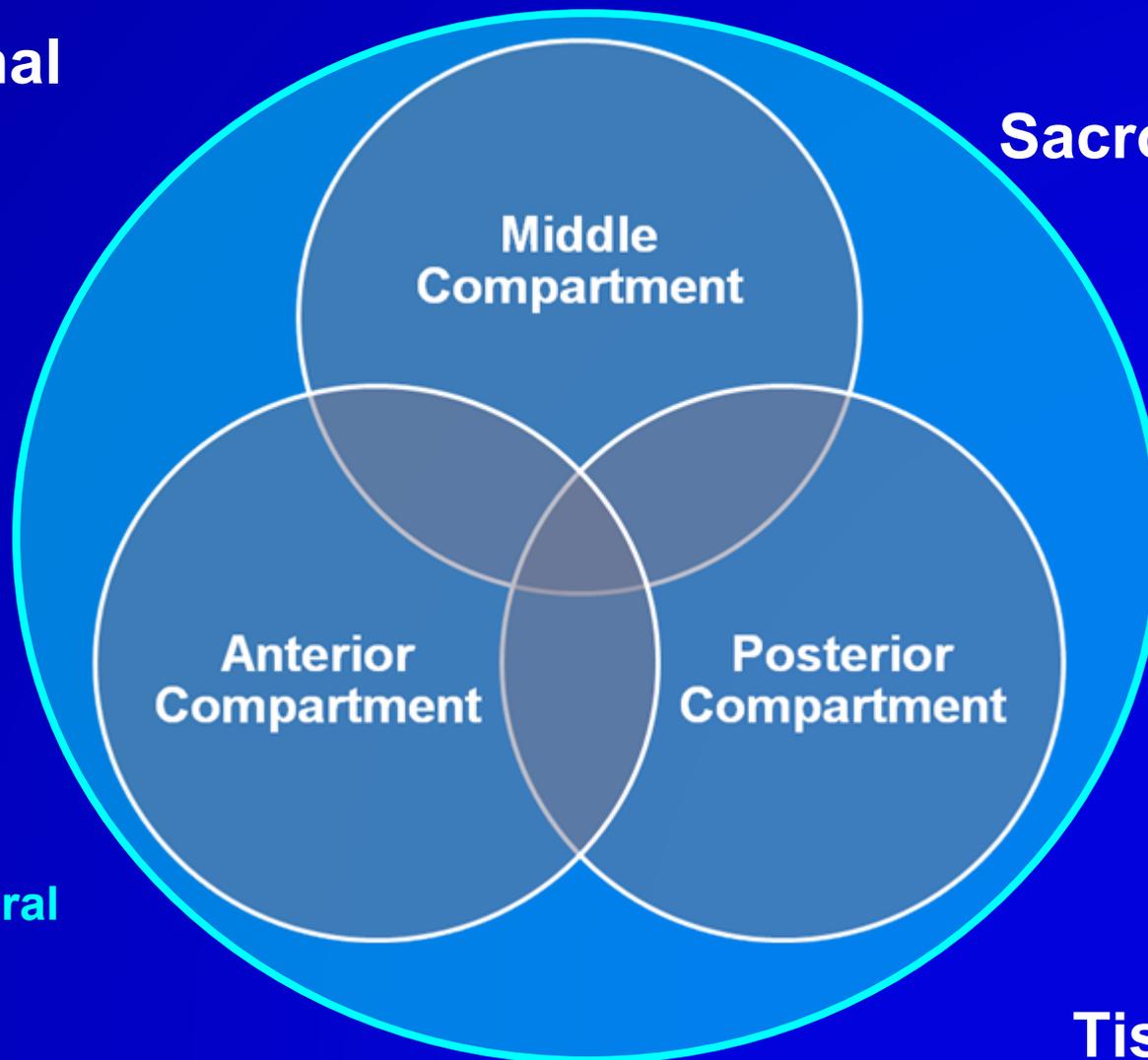
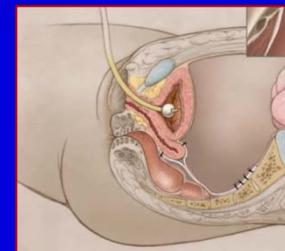


Complicated Disease with Several Surgical Options

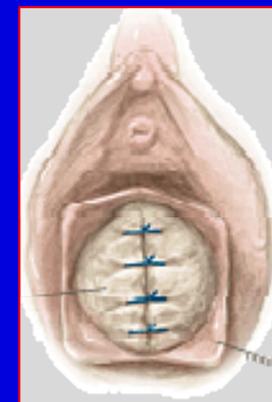
Transvaginal Mesh



Abdominal Sacrocolpopexy

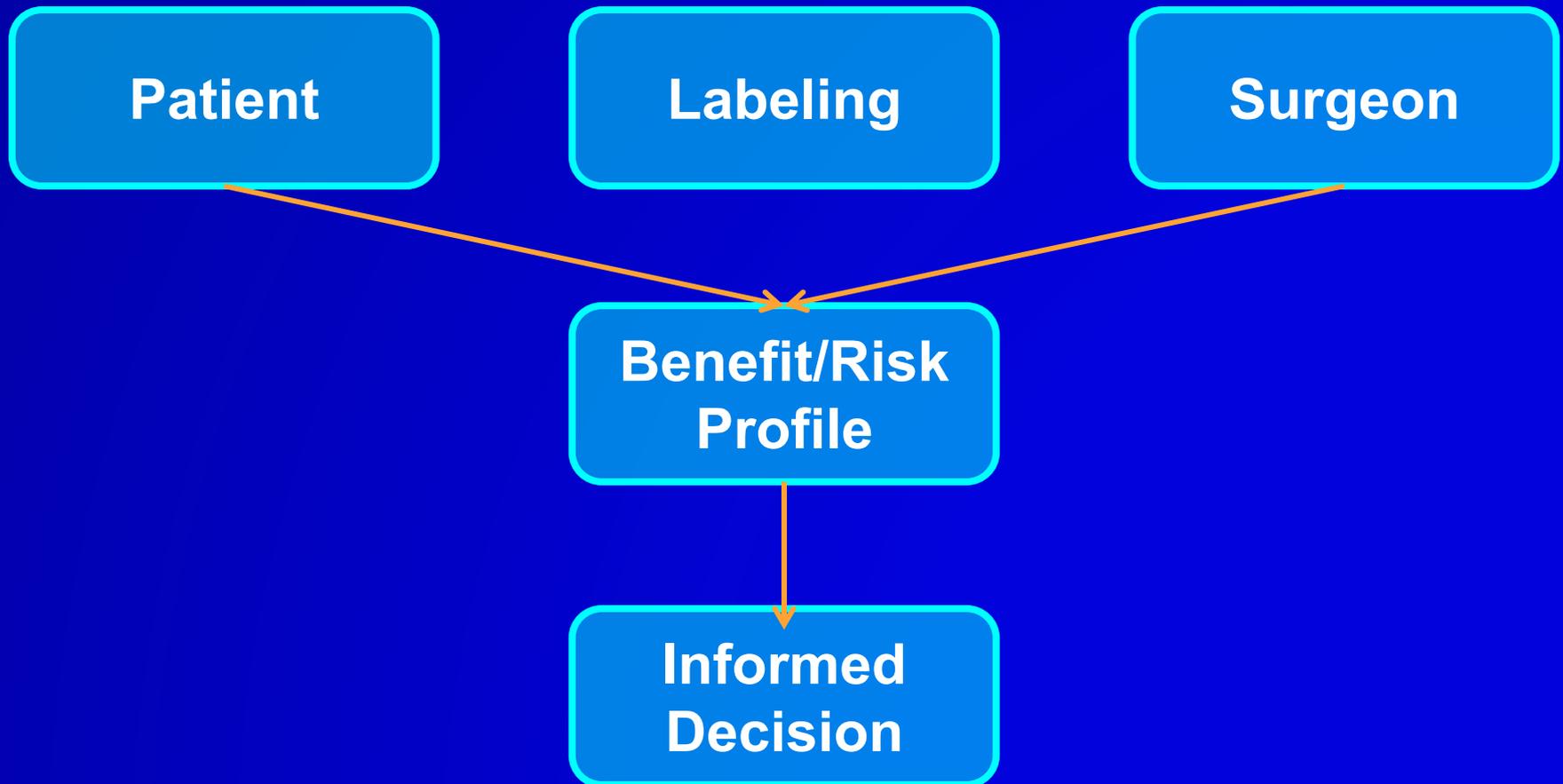


Patient's General Condition



Native Tissue Repair

Pelvic Organ Prolapse Treatment Algorithm

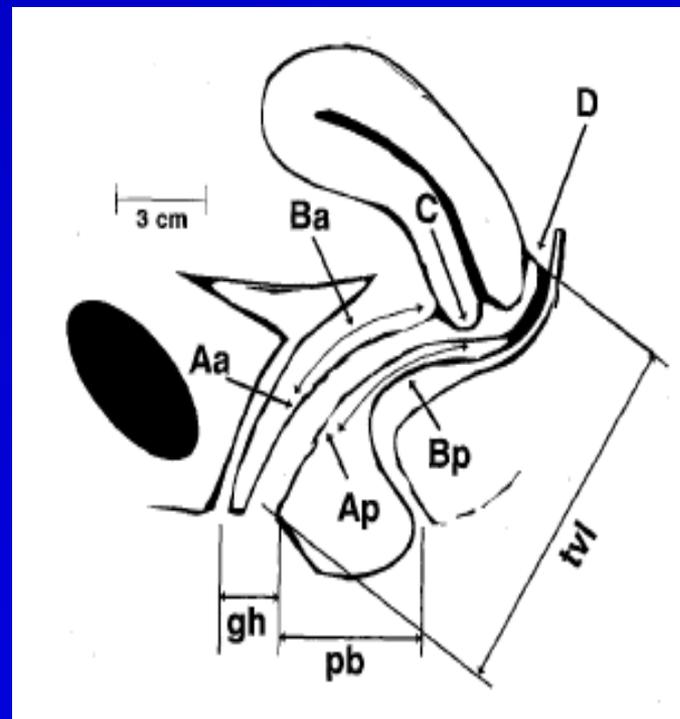


Effectiveness of Transvaginal Mesh

- 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

| RCT | N | Follow-up (months) | Anatomic Cure | | p |
|--------------------|-----|--------------------|-----------------|-------------|----------|
| | | | Mesh | Traditional | |
| Sivaslioglu (2008) | 90 | 12 | 91% Ant | 72% | p<0.05 |
| Nguyen (2008) | 75 | 12 | 87% Ant | 55% | p<0.05 |
| Carey (2009) | 139 | 12 | 81% Ant/Post | 65.6% | p=0.07 |
| Nieminen (2010) | 202 | 36 | 87% Ant | 59% | p<0.0001 |
| Iglesia (2010) | 65 | 9.7 | 40.6 All | 29.6 | p=0.28 |
| Withagen (2011) | 194 | 12 | 90.4 All | 54.8 | p<0.001 |
| Altman (2011) | 389 | 12 | 82.3 Ant | 47.5 | p=0.008 |

RCTs Demonstrate Improvement of QoL Measures of Transvaginal Mesh

| Study | N | Follow-up (months) | Functional Outcome | | p |
|-----------------|-----|--------------------|---|---|----|
| | | | Mesh | Traditional | |
| Nieminen (2010) | 202 | 36 | 'all symptoms' Pre: 100% Post: 28% | 'all symptoms' Pre: 100% Post: 42% | NS |
| Iglesia (2010) | 65 | 3 | PFDI-20 Pre:100 Post:42.9 PFIQ-7 Pre:23.8 Post:4.8 | PFDI-20 Pre:140.6 Post:26.4 PFIQ-7 Pre:38.1 Post:9.5 | NS |
| Withagen (2011) | 194 | 12 | UDI Prolapse Pre:48 Post:5 | UDI Prolapse Pre:50 Post:6 | NS |
| Altman (2011) | 389 | 12 | UDI Pre: 86.9 Post:53.6 | UDI Pre:91.5 Post:53.6 | NS |
| Carey (2009) | 139 | 12 | PSI-QoL mean change Pre- Post: -6.9 | PSI-QoL mean change Pre- Post: -7.8 | NS |

NEJM Study Demonstrates Higher Cure Rate for Transvaginal Mesh

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Anterior Colporrhaphy versus Transvaginal Mesh for Pelvic-Organ Prolapse

| Outcome Measure (at 1 year) | Colporrhaphy n=189 | Mesh Repair 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 |

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

FDA Website: Role of MAUDE



The screenshot shows the FDA website header with the U.S. Department of Health & Human Services logo and the URL www.hhs.gov. Below the header is the FDA logo and the text "U.S. Food and Drug Administration". There is a search bar with a "go" button and an "A-Z Index" button. A navigation menu includes links for Home, Food, Drugs, Medical Devices, Vaccines, Blood & Biologics, Animal & Veterinary, Cosmetics, Radiation-Emitting Products, and Tobacco Products. The breadcrumb trail reads "FDA Home > Medical Devices > Databases". The main heading is "MAUDE - Manufacturer and User Facility Device Experience". A list of bullet points describes the MAUDE database, including its history and search capabilities. A blue callout box highlights a specific warning: "MAUDE data is not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices. Please be aware that reports regarding device trade names may have been submitted under different manufacturer names. Searches only retrieve records that contain the search term(s) provided by the requester."

U.S. Department of Health & Human Services www.hhs.gov

FDA U.S. Food and Drug Administration

[A-Z Index](#) Search [go](#)

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FDA Home > Medical Devices > Databases

MAUDE - Manufacturer and User Facility Device Experience

- MAUDE data represents reports of adverse events involving medical devices. The data consists of voluntary reports since June 1993, user facility reports since 1991, distributor reports since 1993, and manufacturer reports since August 1996. MAUDE may not include reports made according to exemptions, variances, or alternative reporting requirements granted under 21 CFR 803.19.
- The on-line search allows you to search CDRH database information on medical devices which may have malfunctioned or caused a death or serious injury. MAUDE is scheduled to be updated monthly and the search page reflects the date of the most recent update. FDA seeks to include all reports received prior to the update. However, the inclusion of some reports may be delayed by technical or clerical difficulties.
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“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

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

Complication Rates in Perspective: Dyspareunia

| Dyspareunia | Sacrocolpopexy | SSLF | USS | Colporrhaphy | Prolift |
|-------------|----------------|------|------|--------------|---------|
| Baseline | 41 % | - | 21 % | 8 % | 37 % |
| De Novo | 15 % | 36 % | 26 % | 19 % | 17 % |

Adverse Events in Literature

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

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

| Submission Requirements | 510(k) |
|---|--------|
| Bench Data | ✓ |
| Pre-market Clinical Trials | ✓ |
| RCTs | ✓ |
| Physician Training | ✓ |
| Patient and Physician Labeling Controls | ✓ |
| Post-market Clinical Data | ✓ |
| Active Surveillance | ✓ |
| Design Control Detail | X |
| Manufacturing Controls and Inspection | X |

- 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

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