FDA Perspective on Surgical Mesh for Pelvic Organ Prolapse (POP)

September 8, 2010

Gaithersburg, MD

FDA Overview – POP

- MDR Analysis
- Systematic Literature Review
- Clinical Overview
- Concluding Remarks and Panel Questions

Analysis of MDR Reports Associated with the Use of Surgical Mesh for POP Repair

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September 8, 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
  - MDR 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

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 coding of problems 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 reports were removed:
  - Non-urogyn meshes,
  - Duplicate reports,
  - Reports with unknown device specifications,
  - Miscoded reports

Methodology (cont.)

- Remaining reports 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 POP

Year	# of Reports
2008	303
2009	580
2010	620
Total	**1503**

* Previous time period – 2005-2007 approx. 270 reports

Death Reports n=7

Age	Summary of Report's Narrative	Type of Procedure
80	Postoperative heart attack	Vaginal Wall Prolapse
UNK	Postoperative cardiac arrest	POP
61	Bowel perforation and infected hematoma was found 10 days after surgery.	Sacrocolpopexy & Sling Procedure
62	Two days later died of pulmonary embolism	POP & Sling procedure
64	Major vessel injury during procedure, unable to control bleeding	POP
79	Hematoma, Sigmoid perforation, two times laparotomy died 5 weeks later of septic shock	POP
65	Massive pulmonary embolism and died after discharge	Anterior pelvic floor repair, sling procedure & other

Top 10 Adverse Events for POP Reports

Rank	Adverse Events	# of MDRs	Percentile Rate
1	Erosion	528	35.1%
2	Pain	472	31.4%
3	Infection	253	16.8%
4	Bleeding	124	8.2%
5	Dyspareunia	108	7.2%
6	Organ Perforation	88	5.8%
7	Urinary Problems	80	5.3%
8	Neuro-muscular problems	38	2.5%
9	Vaginal scarring (41)/ Shrinkage (2)	43	2.8%
10	Recurrence, Prolapse	32	2.1%

Total number of adverse events is larger than total number of MDR reports because the majority reported more than one adverse event

Most Frequently Reported Required Interventions
n=1503

Intervention	Number
Additional Surgical Procedure	416
Partial or complete mesh explant	182
Hospitalization	72

Summary

- Persistent signal related to the use of surgical mesh for POP

- Serious, life-altering adverse events associated with the use of surgical mesh for POP continue to be reported

Epidemiological Overview of Published Literature on Pelvic Organ Prolapse & Need for Postmarket Studies

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September 8, 2011

Outline

- Background
- Methods
- Findings
- Preliminary results of Medicare study
- Postmarket regulatory options

Background

- FDA purpose of reviewing the literature
  - Since the 2008 PHN there has been increase in MDR reports for urogynecologic procedures
- Objectives of FDA review of the literature:
  - Review safety and effectiveness of surgical mesh used for Pelvic Organ Prolapse (POP) repair and to establish the extent of the literature in support of an appropriate risk/benefit balance.

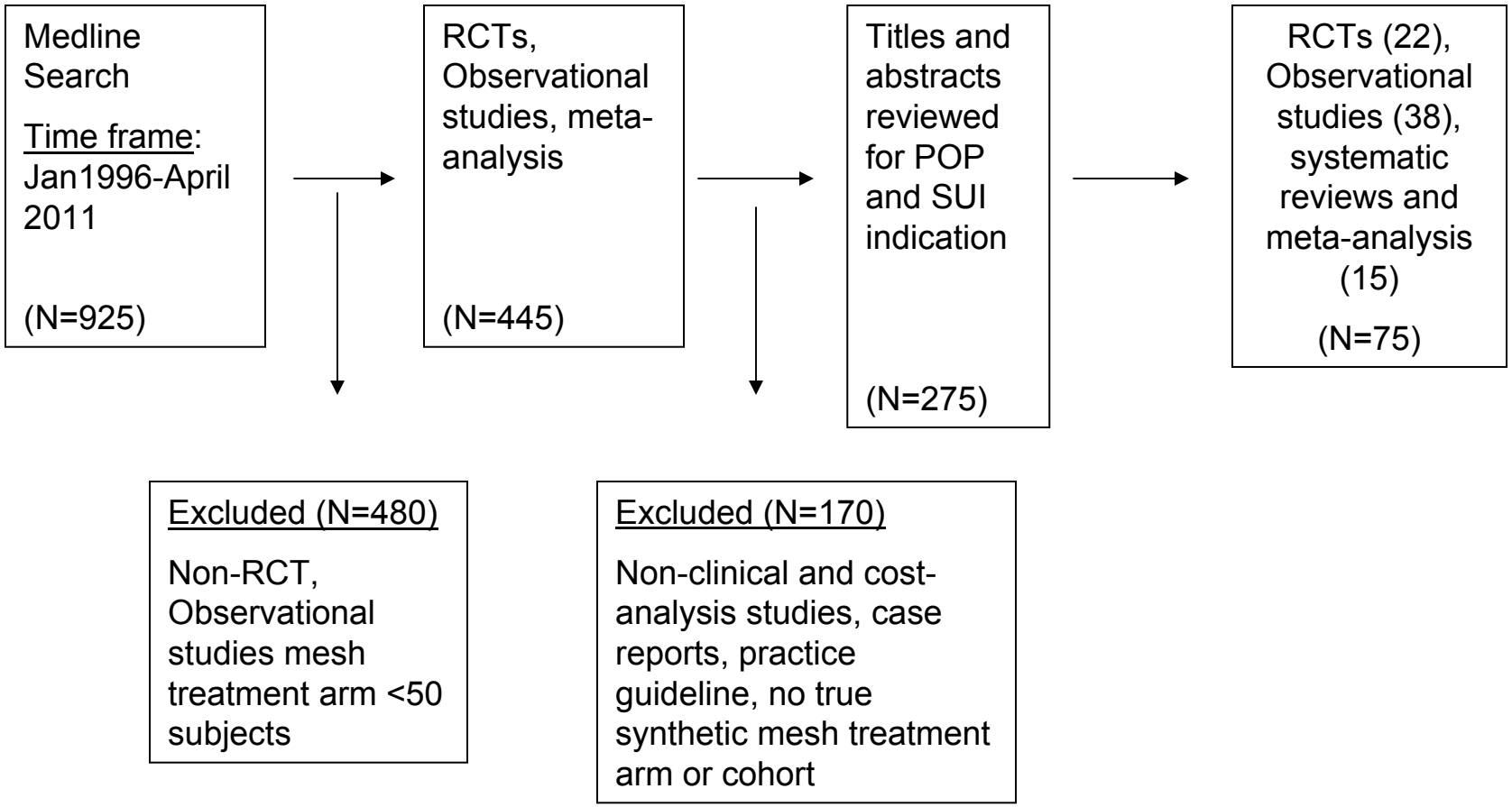
Methods

- Medline database search on the treatment of POP 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

Article Selection



Methods

- Title and abstract review of RCTs indicated that many had methodological limitations
  - Unmasked studies
  - Confounding
  - Non-hypothesis driven trials
  - Differential loss to follow-up

- Thus patients from observational studies and RCTs were grouped together

Methods: Weighted mean percentages of adverse event rates

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

$$\frac{\text{the number of patients with AE}}{\text{the number of patients in treatment group}}$$

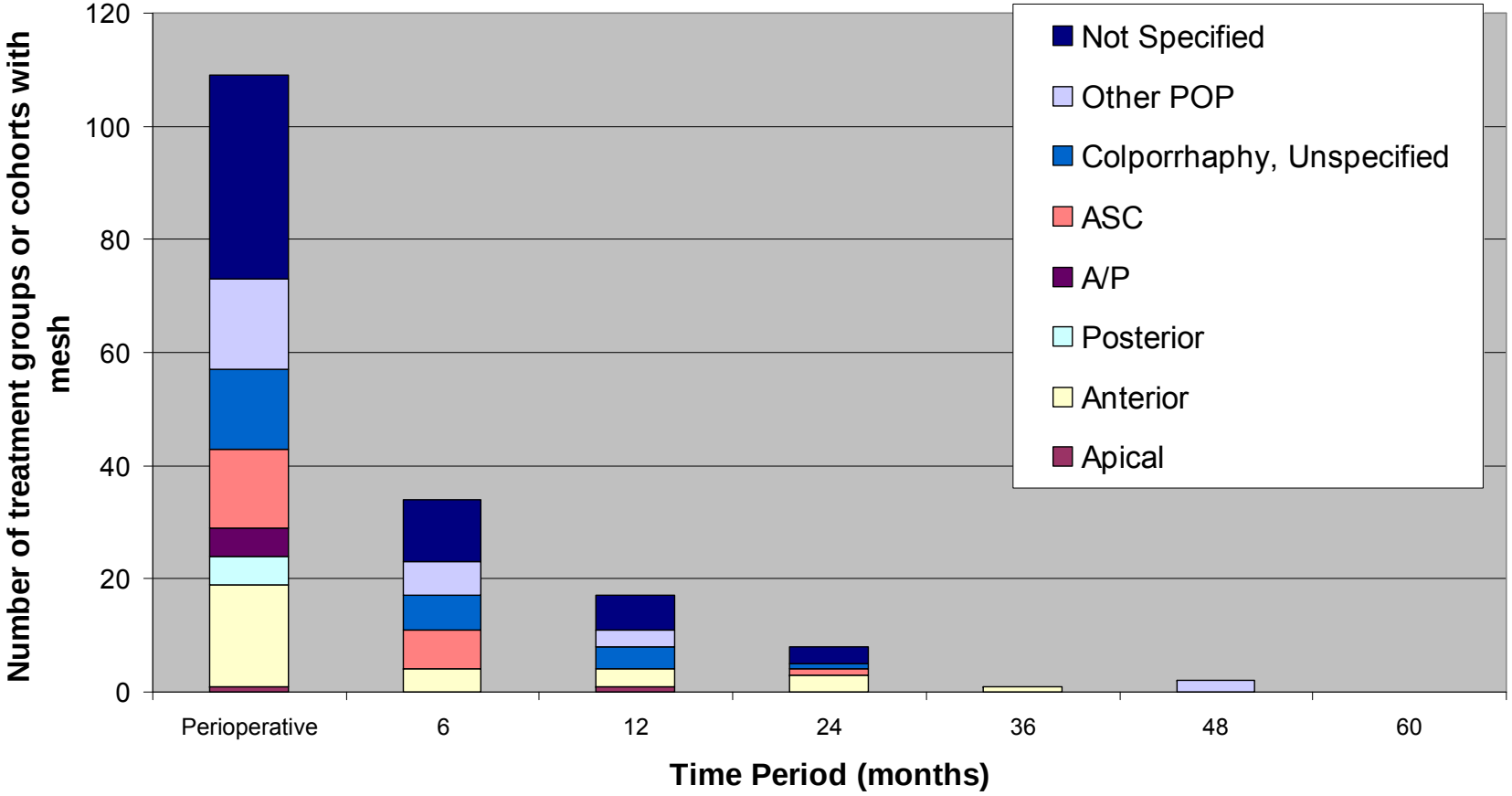
Percentages averaged across treatment groups, weighting the percentages according to the number of patients in each treatment group.

Treatment Cohorts

- There were 115 treatment groups that met our inclusion criteria for POP

- Range of treatment groups 1-3, and range of sample sizes in treatment groups was from 13-577

Number of Surgical Mesh Treatment Groups/Cohorts for POP



Findings

- The proportion of studies by the type of surgical approach included:
  - anterior prolapse repair (39%)
  - abdominal sacrocolpopexy (ASC) (15%)
  - posterior repair (3%)
  - anterior/posterior (3%)
  - apical vaginal repair (1%)
  - not clearly defined (39%)

- The duration of follow-up ranged from perioperative (intraoperative to 48 hours post-operative) to 48 months

Mesh Specific Adverse Events

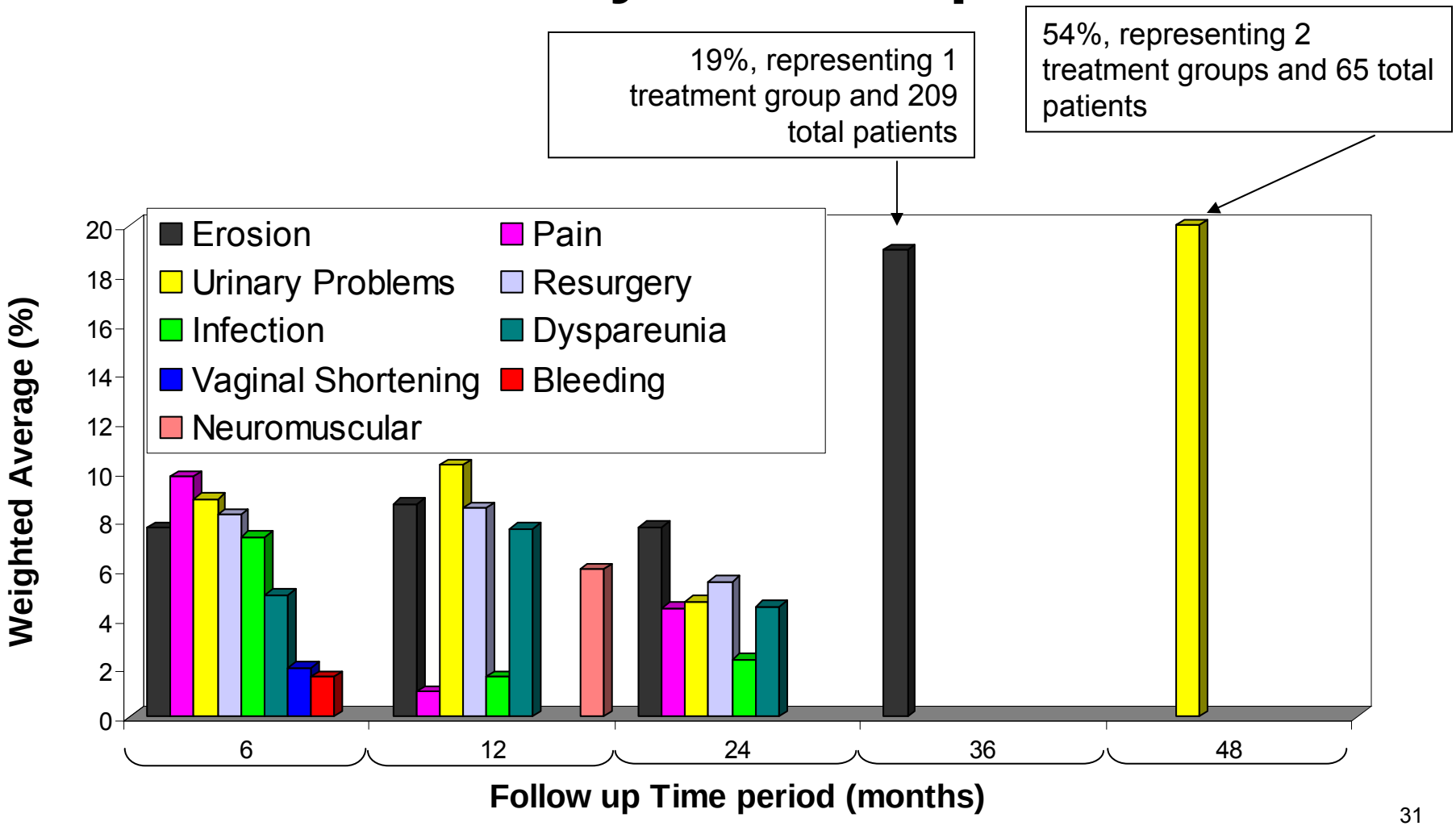
- Erosion is unique to mesh procedures and is not experienced by patients who undergo traditional repair
  - Erosion into the vagina is the most common and consistently reported mesh-related complication following POP repair in the literature
  - The weighted average of mesh erosion reported in the literature ranged from 7.7% to 19%
- Mesh contraction, another mesh-specific AE was reported in the literature

Perioperative Complications

- Organ perforation (2.6%)
- Bleeding (2.4%)
- Hematoma (1.4%)
- Pain (6.0%)
- Infection (7.7%)

* All surgical procedures for POP have associated perioperative risks, other non-mesh procedures are not immune to the complications presented above.

Weighted Mean AE for POP Using Mesh Procedures by Follow-up Period



Other Reported Adverse Events in POP Repair Not Specifically Associated with Mesh

	Range of Weighted Mean Percentages (%)	Range of Follow-Up (months)
Dyspareunia	4.5 - 7.7	6 - 24
Infection	1.6 - 7.3	Peri-operative - 24
Pain	1 – 9.8	Peri-operative - 24
Resurgery	5.5 – 8.5	6 - 24
Urinary Problems	4.7 – 54.2*	6 - 48

*Urinary Problems reported at 54% at 48 months came from 2 treatment groups and 65 total patients

Note: Insufficient information exists in mesh literature to provide quantitative measures of these adverse events among women with “non-mesh” surgeries.

Evaluation of Effectiveness (Mesh vs. No Mesh)

	Anterior	Posterior Repair (all with anterior)
Number of studies	10	4
Showed anatomic benefit	8 unmasked	2 unmasked
	1 masked	0 masked
Did not show anatomic benefit	0 unmasked	1 unmasked
	1 masked	1 masked

Transvaginal Repair Conclusion

- Anterior Repair – Anatomical benefit appears to favor mesh
- Posterior Repair (all with anterior) – Inconclusive if superior anatomic result compared to traditional repair

Limitations of Literature

- Literature on POP repair largely represents studies in which the primary endpoint was ideal anatomic support
- Outcome is not based on a correlation with symptomology
- Results reflect both primary and repeat prolapse repairs
- Most studies involve concomitant surgical procedures
- Adverse events are not the endpoint of interest and inconsistently reported across the studies
- Inclusion/exclusion criteria are incompletely documented
- Majority of studies not evaluator-masked or adequately powered
- Very few studies extend beyond one year

FDA Study on Risk of Repeat or Additional Surgery Following POP Repair Using Mesh

Methods

- Medicare claims database Parts A & B January 1, 2006-December 31, 2010
- Cohort consisted of all women who had POP repair
- Women categorized into two groups depending on whether additional charge code indicating if mesh was used
- **Outcome –** repeat or additional surgery 1 year after initial procedure

Preliminary Findings

- 212,113 had transvaginal POP repair
  - 115,626 (55%) had no mesh
  - 96,487 (45%) had mesh
- Majority were Caucasian (93%) and were between 65-75 years old (57%)
- The Relative Risk of re-surgery for revision was 2.26 (95% CI 2.15-2.40) greater in women who had mesh used in the initial surgery

Limitations of Medicare Data

- Beneficiaries move in and out of dataset
- Claims based
  - Independent billing for each event may be time lag
- Possible misclassification bias of mesh use in initial procedure

Need of Additional Study

- The available scientific literature does not provide evidence that surgical mesh currently on the market and indicated for vaginal POP repair offers a clear improvement in effectiveness compared to traditional repair
  - The rate and severity of mesh-specific adverse events following vaginal POP repair with mesh calls into question the safety of these devices
- There remain unanswered questions for mesh products used for POP

Postmarket Surveillance Studies

- We believe postmarket surveillance studies “522s” are warranted
- These studies can help more immediately answer questions regarding the long term safety and effectiveness of vaginal mesh used for POP repair already on the market

Design Options for 522 Studies

- We may recommend an RCT or prospective cohort study design to compare the device to a control
- Sponsors are responsible for study plan for their devices
  - RCT
  - Prospective cohort
  - Single sponsor registry
  - Multi-sponsor or society registry
  - RCT nested in registry

522 Recommendations

- Women 18 years or older
- Documented pelvic organ prolapse
- Surgery is scheduled
- Adjustment of pertinent risk factors

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Clinical Overview:

Surgical Mesh for Pelvic Organ Prolapse

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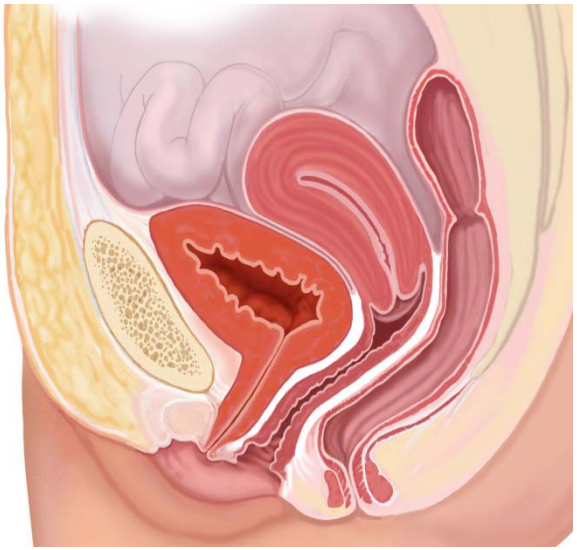
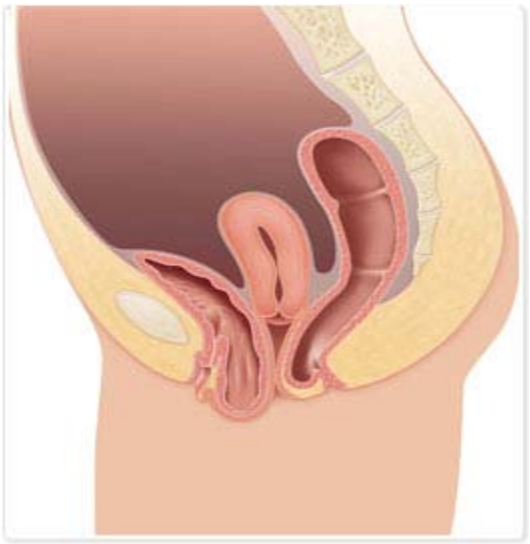
Outline

- Clinical background
- Safety and effectiveness findings in literature
  - overall safety findings
  - abdominal vs. vaginal approach for apical repair
  - vaginal approach for anterior and posterior compartments
- Literature limitations
- Conclusions

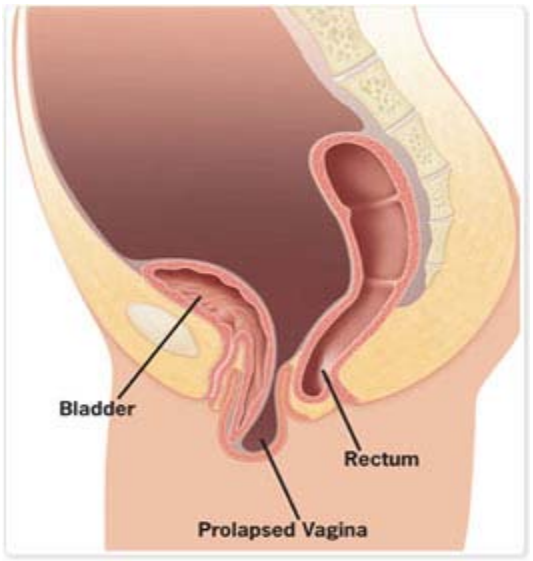
Pelvic Organ Prolapse (POP)



Normal Anatomy



Anterior Vaginal Wall Prolapse (Cystocele)*



Apical Prolapse*

*www.gyneshape.com

Scope of Problem

- National Health and Nutrition Examination Survey (NHANES) 2005-2006 data*
  - 2.9% of women age 18-80 reported symptom of vaginal bulge
- Australian Cohort study 2010†
  - 19% lifetime risk of surgery for POP
- U.K. Cohort Study 2008±
  - 11% reoperation rate for POP surgery at 11 years
    - 39% in the same vaginal compartment
    - 61% in a different compartment

*Nygaard JAMA †Smith Obstet Gynecol ±Price Menopause International

Reasons for using mesh for POP

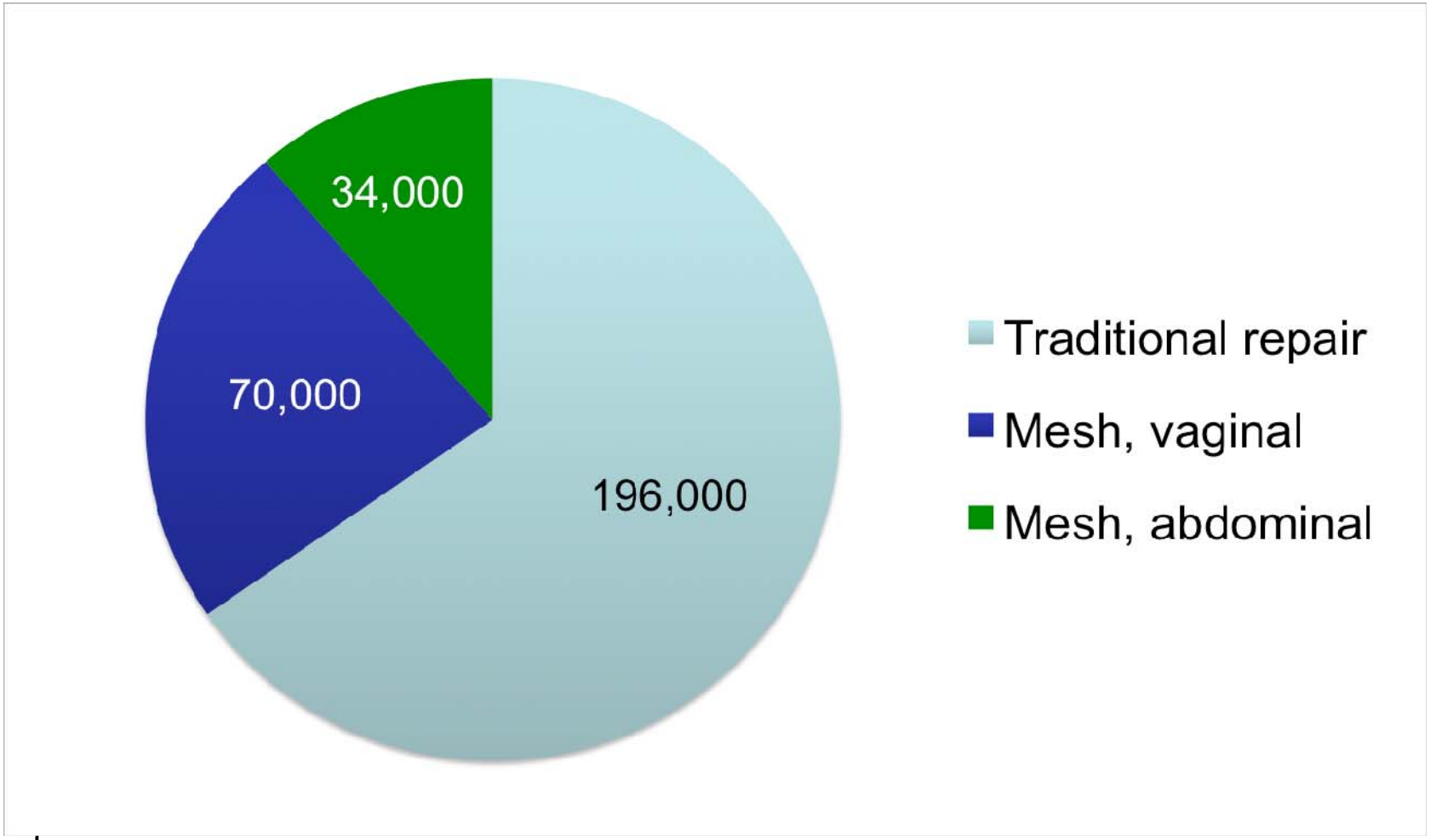
- Increase longevity of repair and decrease need for re-surgery
  - incorporated into clinical practice without clinical validation
  - success with midurethral slings for stress incontinence served as precedent

Repair Approaches

- Vaginal
  - traditional repair (*i.e., suture only, non-mesh*) or mesh augmented for one or more vaginal compartment
  - mesh attached to vaginal wall beneath mucosa and pelvic floor ligaments (anterior, posterior, “total”)
- Abdominal
  - almost exclusively done with mesh (sacrocolpopexy)
  - addresses apical prolapse

POP Repair Surgeries - US Market 2010*

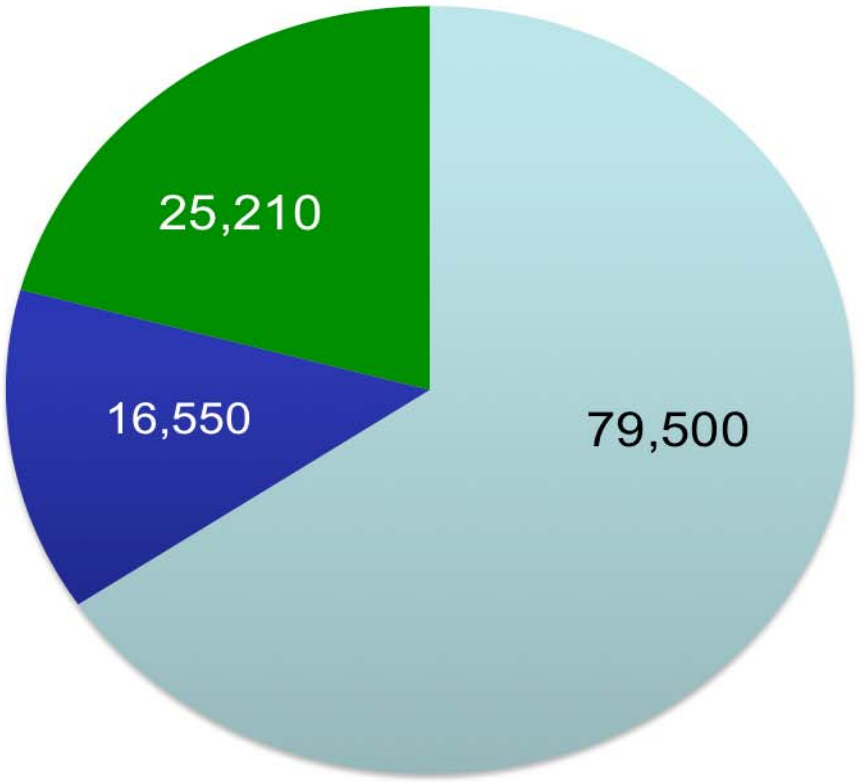
300,000 women



*industry source

POP Mesh Sales 2010*

Total 121,260



Vaginal mesh kits

Synthetic mesh patch

Non-synthetic patch

*US Markets for Soft Tissue Repair 2010, Millennium Research Group, Inc. All rights reserved. Reproduction, distribution, transmission or publication is prohibited. Reprinted with permission.

Safety Signal

- 2008 *Public Health Notification*
- Continued clinical concern
- New MAUDE search 2008 - 2010
  - 1503 reports for POP
  - five fold increase from previous period
  - mesh erosion (also called exposure, extrusion, or protrusion) most often cited adverse event (AE)

Literature Review

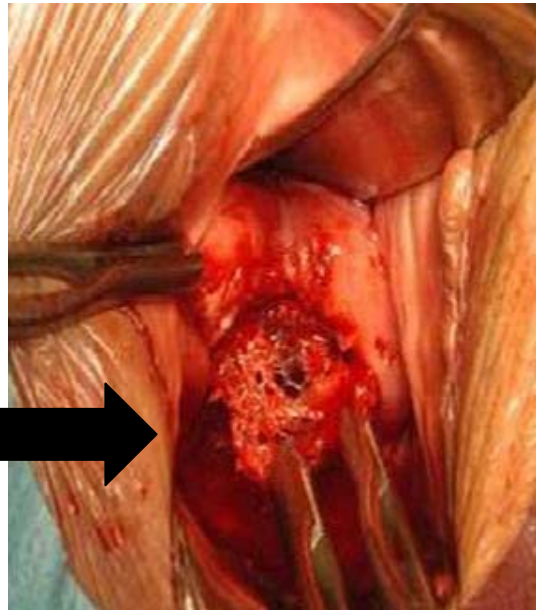
- Evaluate reported safety and effectiveness of surgical mesh for urogynecologic indications
  - rate and severity of adverse events
  - clinical benefit compared to traditional repair

Safety

Mesh Erosion

- Most common and consistently reported AE in literature

Mesh



Risk Factors for Erosion*

- Surgical factors
  - concomitant hysterectomy
  - use of inverted “T” colpotomy incision
  - surgeon experience
- Patient factors
  - age
  - smoking
  - diabetes
- Unclear how much each factor contributes

*Abed Int Urogynecol J 2011

Risk Factors for Erosion (cont.)

- Mesh factors*
  - raw material
    - material type (molecular weight)
    - filament type (mono vs. multi)
  - design
    - weave (woven vs. non-woven)
    - pore size
    - density
    - strength and elasticity

*Earle Surg Clin North Am 2008

Mesh Erosion – Mesh Placed Vaginally

- Summary incidence 10.3% (95% CI, 9.7-10.9%; range 0-29.7%) from 110 studies, n=11,785*
  - timing of diagnosis 6 wks to 12 mo

	Rate	No. studies	No. women
Non-absorbable synthetic	10.3%	91	10,440
Non-synthetic	10.1%	19	1,345

*Abed Int Urogynecol J 2011

Management of Erosion – Mesh Placed Vaginally

- Non-absorbable synthetic mesh erosions (n=795)*
  - 11% treated with excision in office
  - 56% required surgical excision in OR
  - some required 2-3 surgeries to repair
  - sequelae (e.g., pain) may continue despite mesh removal†
- Little reported on non-synthetics (n=35)*
  - half responded to topical treatment
  - remainder not stated

*Abed Int Urogynecol J 2011 †Margulies AJOG 2008

Mesh Erosion - Sacrocolpopexy

- Summary incidence 4% (range 0-12%)

  (27 studies, n=2922±)

  – median follow-up 23 months
  – 3.5% (72/2074) required surgery to manage

  – non-synthetic mesh (median 0%, range 0-0.8%)

  vs.

  – non-absorbable synthetic (median 4%, range 0-12%)

±Jia Int Urogynecol 2010

Mesh Contraction

- Mesh becomes taut, may cause severe pain
  - 12% (80/684) incidence in one series*
    - 2.8% (19/684) required surgical treatment

*Caquant J Obstet Gynaecol Res 2008

Complications Requiring Re-surgery†

	Rate	No. studies	No. women	Mean follow-up
Vaginal mesh	7.2%	24	3425	17 mo.
Sacro-colpopexy	4.8%	52	5639	26 mo.
Traditional repair	1.9%	48	7827	32 mo.

†Diwadkar Obstet Gynecol 2009

Additional AEs

- *de novo* SUI
  - 1 RCT: significantly higher for anterior repair with mesh vs. traditional repair (12% vs. 6% at 1-yr)†
  - no difference in three other trials*
- Other commonly reported AEs
  - pain
  - infection
  - dyspareunia (no difference between mesh and non-mesh vaginal repair reported in 4 trials±)

†Altman NEJM 2011
*Lunardellia Col Bras Cir 2009, Meschia J of Urol 2007, Withagen Ob Gyn 2011
±Sand AJOG 2001, Meschia 2007, Nguyen Ob Gyn 2008, Carey BJOG 2009

Effectiveness

Effectiveness

Most use study endpoint:

"ideal pelvic support" = POP-Q stage 0 - 1
(prolapse > 1 cm above hymen)

However…..

– not correlated with POP symptoms or patient assessment of improvement*

– central anterior wall: interobserver variability 68% agreement (kappa 0.35)†

*Barber Ob Gyn 2009 †Whiteside AJOG 2004

Other Outcome Measures

- Absence of prolapse beyond hymen
  - average number of symptoms increases when prolapse beyond hymen*
- Improvement in prolapse Quality of Life (QoL)
- Re-surgery for recurrence
- Absence of bulge symptoms
  - most associated with patient assessment of improvement and greatest difference in prolapse QoL measures compared to other measures†

*Swift AJOG 2003 †Barber Ob Gyn 2009

Sacrocolpopexy

Effectiveness

Sacrocolpopexy

- Success* (63 studies, n=3,540, followed 6 mo. to 3 years)
  - lack of apical prolapse post-op: 78-100%
  - no post-op prolapse in any compartment: 58-100%
- Three trials directly compare sacrocolpopexy to traditional vaginal repair*
  - all 3: superior anatomic result with sacrocolpopexy
  - 1/3 evaluated symptomatic results: improvement greater in sacrocolpopexy group†

*Nygaard Ob Gyn 2004 †Benson AJOG 1996

Re-surgery for Recurrent Prolapse†

	Rate	No. studies	No. women	Mean follow-up
Sacro-colpopexy	2.3%	52	5639	26 mo.
Vaginal mesh	1.3% 3%♦	24 1	3425 524	17 mo. 38 mo.
Traditional repair	3.9%	48	7827	32 mo.

†Diwadkar Ob Gyn 2009 ♦De Landsheere AJOG 2011

Sacrocolpopexy

(compared to vaginal repair)

Conclusion:

- lower rates of mesh complications
- better anatomic outcomes than traditional repair
- low rates of repeat surgery for recurrent prolapse

Vaginal Apical Repair with Mesh

Effectiveness

Apical

- Multiple case series
  - vaginal repair with mesh often restores anatomy
- 2 RCTs comparing mesh repair to traditional repair
  - multi-compartment repair including apex
- No difference in anatomic outcome

Mesh Erosion - RCTs

Apical

- Erosion 15.6% (5/32)* and 17% (14/83)†

*Iglesia Ob Gyn 2010 † Withagen Ob Gyn 2011

Vaginal Apical Repair with Mesh

Conclusion:

vaginal placement of mesh for apical repair

- *high rates of mesh erosion*
- *no clinical improvement in effectiveness compared to similar non-mesh repair*

Posterior Repair with Mesh

Effectiveness

Posterior

- 1 RCT evaluating single compartment posterior repair with mesh compared to traditional repair*
  - anatomic outcome better with traditional repair
- 4 RCTs evaluating multi-compartment repair (including posterior)
  - 3: no significant difference with mesh†
  - 1: significant anatomic improvement with mesh repair; mesh group less prolapse at baseline‡

* Paraiso AJOG 2006
† Sand AJOG 2001, Carey BJOG 2009, Iglesia 2010
‡ Withagen 2011

Mesh Erosion

Posterior

- Erosion up to 17%
  - potential for serious sequelae

    e.g., rectovaginal fistula, colostomy

Posterior Repair with Mesh

Conclusion:

vaginal placement of mesh for posterior repair

- *high rates of mesh erosion*
- *potential for serious sequelae*
- *no clinical improvement in effectiveness over similar non-mesh repair*

Anterior Repair with Mesh

Effectiveness - RCTs

Anterior

- 11 RCTs comparing to traditional repair (8 single compartment, 2 anterior & posterior, 2 multi-compartment) with 1-yr follow-up
  - 8 used outcome of ideal pelvic support
  - 7/8 unmasked studies found anatomic benefit
  - 3 evaluator masked: 2/3 → no added anatomic benefit with mesh
  - 4 reported on QoL → no added benefit with mesh

Outcome Re-analysis*

Anterior

- Re-analysis of RCT showing low reported success for traditional anterior repair compared to anterior repair with mesh
  - success ≤ stage 1
- Using clinically relevant outcome measure
  - prolapse above or below hymen (success ≤ stage 2)
- High success rates for both using this measure
- No difference in prolapse symptoms or re-operation for recurrence

*Chmielewski AJOG 2011

Mesh Erosion

Anterior

- Erosion up to 17% at 1-year

Recent RCT – Altman, NEJM, 2011

Anterior

- 200 anterior Prolift vs.189 traditional repair
- 1-yr follow-up
- Study success (objective + subjective cure)
  - objective cure: ≤ stage 1 prolapse
  - subjective cure: no complaint of vaginal bulge

Altman Trial - Effectiveness

Anterior

- Study success
  - 60.8% mesh vs. 34.5% non-mesh ($p<0.001$)
- No bulge symptoms
  - 75.4% mesh vs. 62.1% non-mesh ($p=0.008$)

- *No difference in prolapse QoL outcomes*

Altman Trial - AEs

Anterior

- Peri-operative complications with mesh: longer operative time, greater mean blood loss, more bladder perforations
- More *de novo* SUI with mesh (12% vs. 6%)
- Total erosion rate not reported

Altman Trial: Re-surgery at 1-yr

Anterior

	Non-Mesh (n=182)	**Mesh** (n=186)
Repeat anterior repair or SUI surgery	0.6%	2.7%
Surgery for complication	0%	3.2%*
Total	**0.6%**	**5.9%** ($p < 0.05$)

*for mesh erosion

3 Year Follow-up*

Anterior

- Better anatomic results in mesh group
- No difference in symptomatic recurrence

- 19.2% (20/104) mesh erosion rate
- 13.5% (14/104) required mesh resection

*Nieminen AJOG 2010

Re-surgery at 3-yr Follow-up*

Anterior

Re-surgery	Non-mesh (n=96)	Mesh (n=104)
Repeat anterior repair	9.4%	0
Other prolapse	1.0%	5.8%
SUI	9.4%	4.8%
Complication	0	13.5%
Total	**19.8%**	**24.0% (NS)**

*Nieminen AJOG 2010

Anterior Repair with Mesh

Conclusion:

vaginal placement of mesh for anterior repair

- *high rates of mesh erosion & de novo SUI (1 trial)*
- *better anatomic result (maybe)*
- *mixed data on symptomatic results*
- *no difference in QoL outcomes*
- *possible increase in re-surgery compared to non-mesh repair*

Data Limitations

- Outcome measure
- Lack of masked evaluations
- Primary and repeat surgeries included
- Multiple concomitant procedures
- Inconsistent AE reporting
- Data for subset of products
- Lack of long-term follow-up

Conclusions from Literature

- Vaginal repair with mesh is main concern
  - serious AEs are *not* rare
  - effectiveness not superior to traditional repair (possible exception for anterior repair)
  - little known about long term implications
  - safety and effectiveness in question
- Sacrocolpopexy less concerning
  - lower rates of mesh complications
  - excellent anatomic outcomes
  - low re-surgery rates for recurrent prolapse
  - safety and effectiveness demonstrated in literature

Regulatory concern:

How good is vaginally placed mesh for POP repair?

- New products
  - need to establish safety profile and benefit, in comparison to similar non-mesh repair
  - the 510(k) paradigm calls for comparison to legally marketed device (predicate)
  - class III (premarket approval) allows for appropriate comparison → need to up-classify

Regulatory concern:

How good is vaginally placed mesh for POP repair?

- Currently marketed mesh products
  - additional clinical data also needed
  - up-classification to Class III & PMA requirements (incl. clinical data) would apply
  - postmarket surveillance studies should start now
    If designed properly, can satisfy future PMA

→ Panel: Discuss FDA's evaluation of literature, proposed regulatory strategy

Surgical Mesh for POP

Recap and Panel Questions

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FDA Wrap-Up

- Re-cap last 3 speakers
- Regulatory considerations
- New strategy, moving forward
- Introduce panel questions

FDA's MAUDE Database

What does it tell us about Adverse Events?

- Medical Device Reports (MDR) reports *increased* from 2005-07 to 2008-10
- Number of MDR reports on mesh/POP *increased* five-fold from 1st to 2nd reporting period
- Identifies vaginal contraction/shrinkage, previously unreported complication

FDA Epidemiology Review

- serious morbidity, unique to mesh
- limited long-term outcomes data

  …both safety *and* effectiveness
- postmarket studies needed to fill in information gaps

FDA Clinical Findings

- high rate of SAEs unique to mesh
  (e.g. vaginal mesh exposure)
- mesh augmentation does not improve clinical outcomes
- long-term safety and effectiveness unknown

Device Classification: Premarket Review

- Class I: usually exempt from 510(k)
- Class II: usually requires 510(k)
  - vaginal mesh for POP
- Class III: usually requires PMA

What is the situation today?

- Since 2002 to date, FDA has cleared >100 510(k)s for mesh products indicated for POP repair
  - none based on clinical data
  - published studies now indicate serious risks, no clinical benefit (v. non-mesh repair)

- Need to know: Does the use of mesh improve clinical effectiveness compared to traditional (non-mesh) repair, sufficient to outweigh the additional risks?

  A randomized clinical trial (RCT) could answer this question.

In Class II, can we get the info we need?

Consider the available Class II "Special Controls"

- Performance standards
- Postmarket surveillance
- Patient registries
- Guidelines (including clinical data, labeling)

In Class II, can we get the info we need?

510(k) standard is "substantial equivalence"

→…only needs to be as good as device on the market.

→ *That's not good enough.*

Where to go from here?

- Clinical trial showing substantial equivalence not sufficient to ensure safety and effectiveness of vaginal mesh for POP

- Reclassification would allow for assessment of reasonable assurance of safety and effectiveness via a RCT with a non-mesh control arm

Class III Premarket Approval

What kind of clinical trial is needed?

- targeted patient population
- clinically meaningful endpoints
- adequate patient follow-up (long term outcomes)
- the right research question
  - no-mesh control arm
  - superiority test

FDA Strategy: Premarket + Postmarket

- Premarket
  - Reclassify from Class II to Class III
    - Proposed Rule with draft PMA guidance
    - Final Rule and final guidance, with effective date
    - probably 18 months – 2 yrs to complete
  - When finalized, Class III requirements would apply to *both* new devices *and* POP mesh already cleared for market
    - During interim, cleared products available

FDA Strategy: Premarket + Postmarket

- Postmarket
  - Issue 522 orders to mfrs of surgical mesh, conduct postmarket study
  - 522 order would apply to products already being marketed

Thank You!

Questions?

Panel Discussion Questions

Question 1: Part a

Risk-Benefit of Vaginal Mesh for POP 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 the safety of vaginal mesh for POP repair?

Question 1: Part b

Considering the available evidence, is there reasonable assurance that vaginal mesh for POP repair is effective?

Question 1: Part c

Considering the available evidence on safety and effectiveness, do the risks outweigh the benefit?

Question 2: Part a

Reclassification of Vaginal Mesh for POP Repair

Are clinical studies needed for premarket evaluation of vaginal mesh products for POP repair?

If yes, what type of clinical studies?

Question 2: Part b

Class II Special Controls – Are they sufficient?

Question 2: Part c

Should vaginal mesh for POP remain in Class II (Special Controls) or be reclassified into Class III (Premarket Approval)?

Question 3

Vaginal Mesh for POP Repair: Postmarket Studies

Are 522 postmarket studies needed on currently marketed vaginal mesh for POP repair?

If so, what type of studies?

Question 4

Abdominal Sacrocolpopexy (ASC)

Are the safety & effectiveness of *abdominal* placement of surgical mesh for POP repair of apical prolapse already well established?

Question 4: Part a

Should *new* mesh products for abdominal sacro-colpopexy be supported by clinical performance data?

If yes, what type of clinical studies?

Question 4: Part b

Should 522 postmarket clinical studies be conducted on *currently* marketed mesh products for abdominal sacro-colpopexy?

If yes, what type of clinical studies?

Thank You!

Back Up Slides

Perioperative Complications

- Bleeding requiring transfusion – 0.5-2.5%
- Rectal injury – 0.6-0.8%
- Infection – 4.1%
- Pain – 2.0%

Long Term Complications

- Dyspareunia 1-3.2% up to 5 years post-op