



**Oral Presentation to
Obstetrics and Gynecology Devices Panel
September 8, 2011**

Good afternoon, ladies and gentlemen. My name is Dr. Saralyn Mark. I am an Adjunct Associate Professor of Medicine and Obstetrics and Gynecology at both Yale University and Georgetown University Schools of Medicine. Today, I am speaking as a Consulting Scientific Policy Advisor for Cook.

Cook is a privately-held manufacturer of products for surgery, gynecology and other medical specialties, with more than 10,000 employees worldwide, including 8,000 employees in North America. For more than 13 years, Cook has been providing biologically-derived grafts that are not cross-linked, including grafts for pelvic organ prolapse (also known as "POP") in over 10,000 patients. Given its background, Cook respectfully submits the following comments for your consideration.

Surgeons have been using synthetic mesh and biologically-derived grafts for over 10 years to improve upon the outcomes associated with standard colporrhaphy. However, FDA's recent report has raised legitimate concerns about these products.

To place the Report in context: Successful outcome of any implant procedure depends on three factors: (1) assuring that the patient is a suitable candidate, (2) performing the procedure correctly, and (3) choosing the appropriate product.

While the Report addresses the safety and effectiveness of different procedures, it only briefly acknowledges that there are significantly different types of products.

Although the Report mentions both non-absorbable and absorbable synthetics, it does not distinguish between chemically cross-linked vs. non-crosslinked biologic grafts.

As a result, Cook has conducted a thorough review of the literature on POP repair with respect to these four fundamental material types. We reviewed the literature on tissue response and on clinical outcomes. Please note that Cook's products are one of several non-crosslinked biologic grafts on the market. Our review focused on material types, not specific products, as we believe that analysis by material type is more instructive than analysis by individual product. The literature review has been submitted to FDA and the Panel and is available on FDA's website. The remainder of my presentation summarizes the review and our conclusions.

Most non-absorbable synthetic mesh for POP repair is made of Type I polypropylene. With Type I polypropylene, compact fibrous tissue surrounds the mesh, which is postulated to provide a strong bond between it and adjacent tissue. However, there is a body of literature that suggests

that the ultimate tissue response is that of a foreign body, such as: granulation tissue, limited neovascularization, eventual fibrosis, and encapsulation.

Absorbable synthetic mesh has an initial response similar to the response to the non-absorbable mesh. Unfortunately, the patient's cells hasten the degradation of the mesh. So absorbable synthetic mesh products do not provide long-term mechanical support, are not in widespread use, and will not be discussed further.

Cross-linked biologic grafts are processed using chemical agents to bond or "cross-link" collagen fibers together in hopes of inhibiting the rate of degradation. However, the normal infiltration of the body's own cells into the graft is significantly decreased. Studies show that inflammation gradually gives way to a foreign body reaction and encapsulation. The tissue response of chemically cross-linked graft material is much like a synthetic.

Non-crosslinked biologic grafts are minimally processed to remove cells without cross-linking the collagen. They provide both mechanical strength and a collagen scaffold that permits cellular infiltration, proliferation, and remodeling of the patient's tissue. The scaffold is gradually repopulated by the patient's cells. In its final state, the structural defect is repaired and reinforced as the original graft material is replaced by well-organized connective tissue and a normal vascular supply.

Cook reviewed synthetic mesh products and standard colporrhaphy by examining the references cited in FDA's report. Additionally, Cook reviewed the clinical literature for the past 15 years for articles describing biologic grafts used in POP repair. For every article, the incidence rates of the following five parameters were reviewed: (1) erosion, (2) pain including dyspareunia, (3) graft-related infection, (4) persistence or recurrence of prolapse based on objective measures (such as the POP-Q score), and (5) symptomatic recurrence.

Cook's review presents extensive data on the five parameters for the different material types. However, when comparing different types of materials, three objective measures - erosion, infection, and objective measurement of recurrence - allow for a more standardized comparison than the subjective measures of pain and symptomatic recurrence. Thus, these next three slides focus on erosion, infection and objective recurrence for the three widely-used material types. Rates are reported as non-weighted averages of the incidence rates reported in the literature. Reports were weighted equally, in part to prevent very large studies from unduly influencing the analysis.

As can be seen, non-absorbable synthetic mesh products had a 10% erosion rate, while cross-linked biologics had 6.2% rate. Repairs with non-crosslinked biologic grafts had the lowest erosion rate at 1.2%.

Infection rates associated with all three material types were similar to or lower than the 4.0% infection rate associated with colporrhaphy.

Repairs with all three material types had lower rates of objective recurrence than colporrhaphy. Repairs with non-absorbable synthetic mesh had the lowest objective recurrence rate. The rate

for repair with non-crosslinked biologic grafts was approximately one-half of the rate for colporrhaphy.

These differences in clinical outcomes between materials are consistent with the body's local tissue response. The histological literature suggests that the body responds to non-absorbable synthetic mesh and chemically cross-linked biologic grafts as foreign bodies. The body responds to non-crosslinked biologic graft materials by remodeling it into organized tissue, substantially reducing the risk of long-term foreign body response.

The data show that the different material types have different risk profiles. To illustrate this difference, the next slide compares data on all five outcomes associated with non-absorbable synthetic mesh products and non-crosslinked biologic grafts.

Both types of materials offer decreased rates of pain, objective recurrence and symptomatic recurrence compared to colporrhaphy. Non-crosslinked biologic grafts also offer decreased rates of infection. The clearest difference is in erosion rates, with repair using non-absorbable synthetic mesh products having a 10% rate and repair using non-crosslinked biologic grafts having a 1.2% rate.

It is also important to note the significance to the patient in management of erosion and recurrence. Erosion with a non-crosslinked biologic graft can be managed with topical medical treatment, rather than one or more operative revisions. Recurrence of the prolapse with a non-crosslinked biologic graft does not involve working around or removing the graft. The graft remodels into organized tissue and the fascial planes are preserved, thus making it easier to perform a surgical revision, if necessary.

In summary, the literature review shows important differences exist in the risk profile among the four types of materials.

- Tissue responses are different.
- Erosion rates are different.
- Recurrence rates are different.
- Management of complications is different.

Cook's review shows that the literature strongly suggests that important differences exist between materials in terms of tissue response and clinical outcome. The literature provides reasonable assurance of safety and effectiveness of non-crosslinked biologic grafts, such as those provided by Cook and other companies.

Therefore, Cook believes that non-crosslink biologic grafts should remain as Class II devices for the following reasons:

- The grafts are not permanent implants, but are replaced by the patient's organized tissue in less than 12 months.
- The grafts are not for use in supporting or sustaining human life.
- Any complications associated with grafts can be managed with less risk to the patient.

- The grafts have a low overall risk profile.
- The grafts have an improved safety and effectiveness profile compared to colporrhaphy.

So in summary, Cook urges FDA and the Panel to consider this information when deliberating on recommendations concerning materials for POP repair.

Thank you for considering our views.

The Safety and Effectiveness of POP Repair Depends on the Type of Biomaterial Used

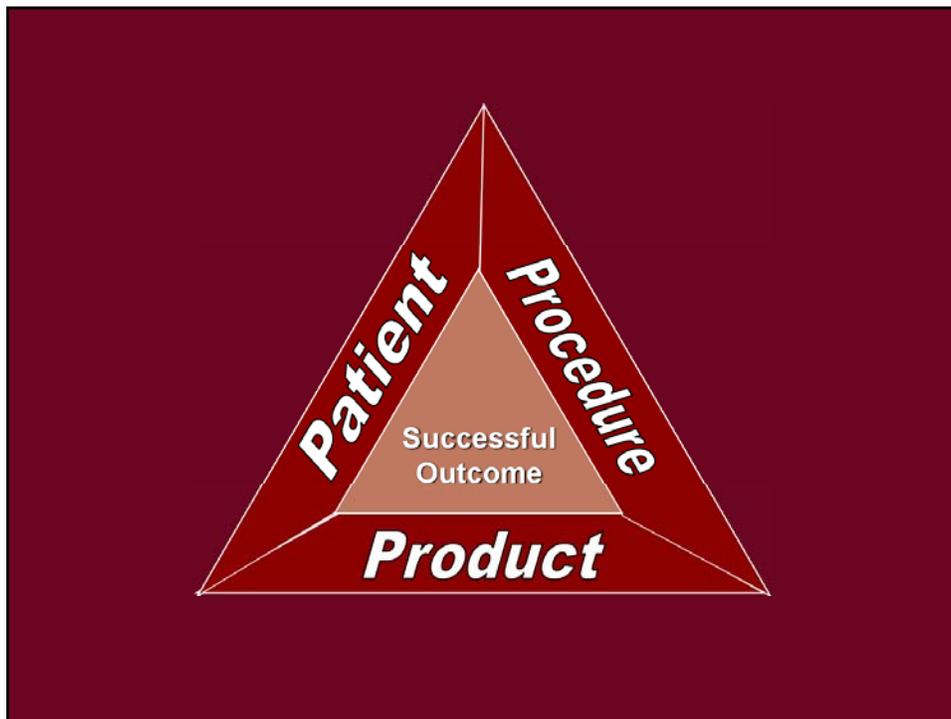
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COOK MISSION

Cook is dedicated to bold leadership in
pioneering innovative medical solutions to
enhance patient care worldwide.





Types of Biomaterials

| Synthetic Mesh | Biologically-Derived Grafts |
|----------------|-----------------------------|
| Non-Absorbable | Cross-linked |
| Absorbable | Non-crosslinked |

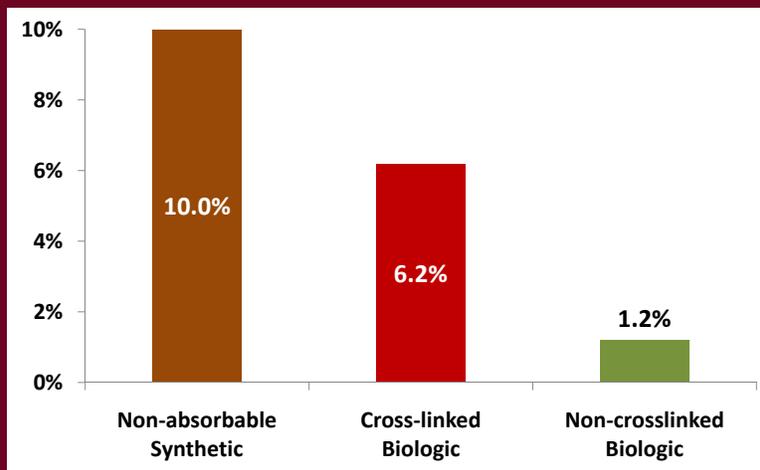
Tissue Response

| Synthetic Mesh | Biologically-Derived Grafts |
|---|---|
| <p><i>Non-Absorbable</i></p> <ul style="list-style-type: none">• Strong bond of mesh and tissue• Foreign body response• Granulation• Limited neovascularization• Eventual fibrosis | <p><i>Cross-linked</i></p> <ul style="list-style-type: none">• Chemically-modified collagen inhibits degradation• Infiltration of cells into graft is significantly decreased• Foreign body response |
| <p><i>Absorbable</i></p> <ul style="list-style-type: none">• Patient's cells hasten degradation of mesh• No long-term mechanical support | <p><i>Non-crosslinked</i></p> <ul style="list-style-type: none">• Infiltration and proliferation• Gradual remodeling• Well-organized connective tissue• Normal vasculature |

Literature Review

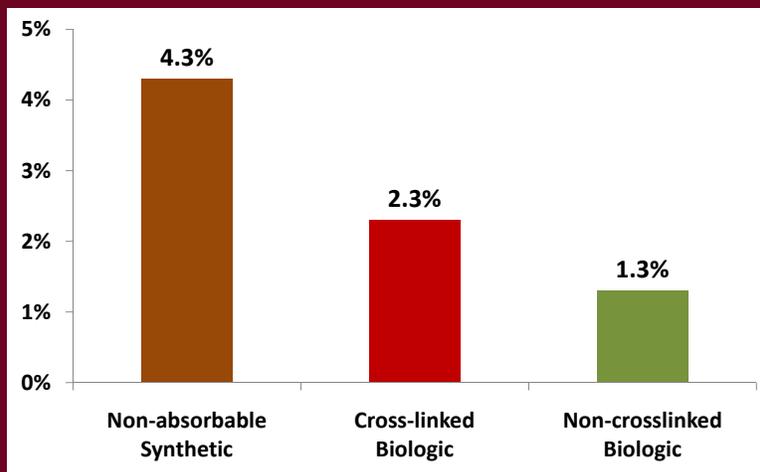
- References from FDA's report for synthetic mesh and colporrhaphy
- 15 years for articles describing biologic grafts
- Five parameters reviewed for incidence rates:
 1. Erosion
 2. Pain
 3. Infection
 4. Objective recurrence (e.g., POP-Q, Baden-Walker)
 5. Symptomatic recurrence

Average Rates of Erosion



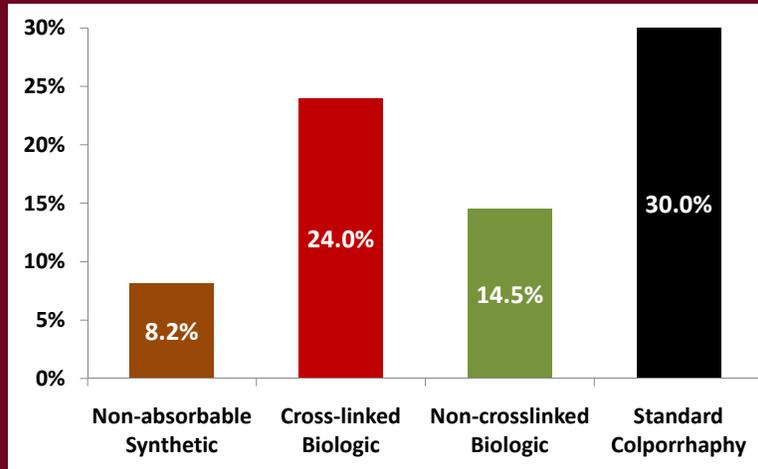
Source: Cook Literature Review

Average Rates of Infection



Source: Cook Literature Review

Average Rates of Objective Recurrence



Source: Cook Literature Review

Local Tissue Response

Tissue responds to different materials in different ways.

SUMMARY: Risk Profile

| | Non-absorbable Synthetic | Non-crosslinked Biologic | Colporrhaphy |
|------------------------|--------------------------|--------------------------|--------------|
| Erosion | 10.0% | 1.2% | <i>n/a</i> |
| Pain | 11.6% | 15.4% | 21.5% |
| Infection | 4.3% | 1.3% | 4.0% |
| Objective Recurrence | 8.2% | 14.5% | 30.0% |
| Symptomatic Recurrence | 13.9% | 15.1% | 20.3% |

Source: Cook Literature Review

Management of Erosion and Recurrence

- Erosion
 - Managed with topical medical treatment
 - Does not require one or more operative revisions
- Recurrence
 - Does not involve working around or removing the graft
 - Graft remodels into organized tissue
 - *Fascial planes are preserved*
 - *Easier to perform a surgical revision*

Summary

- Important differences in risk profiles exist among materials:
 - Tissue responses
 - Erosion rates
 - Recurrence rates
 - Management of complications

Conclusions

- The grafts are not permanent implants, but are replaced by the patient's organized tissue in less than 12 months.
- The grafts are not for use in supporting or sustaining human life.
- Any complications associated with grafts can be managed with less risk to the patient.
- The grafts have a low overall risk profile.
- The grafts have a improved safety and effectiveness profile compared to colporrhaphy.