Prolapse Surgery

How to Handle
“Innovations”

Polypropylene Is Not Inert in the Human Body

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Long Beach Memorial Medical Center
Medical Marketing versus Science with New Procedures and Grafts

Polypropylene Mesh Grafts: What Influences Erosion vs. Tissue Incorporation?
What is the Major Issue?

Traditional Surgery with Suture vs.
“Innovative” Surgery with Mesh Kits ($1000-3000 per kit)

Physicians need to know relative benefits and risks using evidence based medicine: Which mesh or procedure is best?
Should Mesh Be Used In All Patients?

- 37-100% of traditional anterior repairs are successful
- Recent reports indicate 81-88%
- 37-100% of primary patients have mesh inserted they do not need
- 10% return to the operating room for removal with substantial morbidity

Maher C et al. *Int Urogynecol J Pelvic Floor Dysfunct.* 2006;17:195-201.
Cystocele Repair
Suture vs. Mesh

- Randomized, prospective comparative trials
- Either no statistically significant difference or—
- A significant difference for anatomical correction for the mesh
- But, quality of life questionnaires are not significantly different

Nguyen JN, Burchette RJ. Obstet Gynec 2008;111:891-898
Standard Anterior Repair vs Anterior Repair with Mesh

- Prospective, randomized, controlled clinical trial
- Ant/post repair with mesh vs traditional colporrhaphies
- 70 patients in each group
- After 1 year, no statistically significant difference between groups for recurrent prolapse
- Same rate of dyspareunia

Cystocele Repair
Suture vs. Mesh

- There is no Level 1 evidence to support the use of mesh in any vaginal compartment
- International societies and individual authorities are stating: “There is no evidence that mesh should be used in all prolapse surgeries”.

FitzGerald MP. J Urol 2010;183:430-432.
Review the Evidence for Graft Usage in Pelvic Prolapse

- Jia, X et al. Systematic review of the efficacy and safety of using mesh or grafts in surgery for anterior and/or posterior vaginal wall prolapse

- NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE (of the United Kingdom)
  224 pages! June 08

- www.NICE.org.uk
“Too few data reported for any of the efficacy outcomes”
“Too few data on safety outcomes”
“No firm conclusions could be drawn about the effectiveness of any of the mesh/graft types compared to no mesh for anterior and/or posterior repair”
In the Early 1990’s We Stepped Over a Very Important Line

<table>
<thead>
<tr>
<th>TRADITIONAL</th>
<th>“INNOVATIVE”</th>
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<tbody>
<tr>
<td>Anterior repair</td>
<td>Prolift™</td>
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<tr>
<td>Kelly plication</td>
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<tr>
<td>Posterior repair</td>
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<td>McCall culdoplasty</td>
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<td>Elevate™</td>
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<td>Avaulta™</td>
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Who Controls Our Thoughts and Who Teaches Us New Surgical Procedures?

- Previously, physicians and science
- Now, industry control and marketing
- Teaching by industry representatives in the operating room
- Sometimes the company sends a physician proctor
What Kinds of Synthetic Grafts are used in Prolapse Surgery?

- **Type I: Macroporous:**
  - Pores >75 microns
  - Most prolapse grafts in current use, Marlex

- **Subdivision by mesh weight**
  - Light weight = <50-60 gm/m²
  - Heavy weight = >60 gm/m²

Amid P. Hernia 1997;1:15-21
What Kinds of Synthetic Grafts are used in Prolapse Surgery?

- **Type II: Microporous:**
  - Pores =/<10 microns
  - Gore-Tex

- **Type III: Microporous with macroporous components**
  - ObTape, Mersilene

- **Type IV: Totally nonporous**
  - Silastic
What is the Best Mesh?

- Macroporous
- Polypropylene vs. polyester (polyethelyene terephthalate)
  - Mersilene (reconfigured)
- Light weight = <50-60 gm/m²
  - Most currently used meshes
- Heavy Weight = >60 gm/m²
  - Marlex (95)
  - Surgipro SPM, IVS (85)
Anatomy of a Macroporous Monofilament Mesh

INTERSTITIUM

PORE >75 µ

LARGE CALIBER MONOFILAMENT POLYPROPYLENE FIBERS
About 150 µ diameter
Monofilament Mesh Weaves

Which one has the greatest surface area?
A Microporous Multifilament Mesh With Macroporous Components (IVS)

- Multifilament small diameter fibers 20-40 µ
- Greatly increases surface area
- Weight = 85 g/m²

A Microporous Multifilament Mesh: Heat Welded (ObTape)

Non-Knitted Non-woven

Multi-filament with greatly increased surface area

“Cul de Sac” Blind pores

Multi-filament with greatly increased surface area

FDA 510 (k) Clearance Process for New Devices (Mesh)

- The FDA does not approve new devices or surgical procedures
- The FDA clears devices for marketing
- The manufacturer must claim similarity to a predicate device that the FDA has already cleared
- Must be similar in planned usage and technological characteristics

Guidance for the preparation of a premarket notification application for a surgical mesh. March 2, 1999. HHS Publication FDA 95-4158
Where are the similarities?
Manufacturer’s Requirements
For FDA Clearance

- No need to show rates of success or adverse events
- No need to study in animals or humans
- No need to prove that it treats what it is intended to treat
- Only need to claim, but not prove, that it is substantially equivalent to a material previously cleared for marketing by the FDA
- Manufacturers want you to believe that their product is FDA approved and inert
Clinical Graft Material Concerns

- Related to its foreign body nature
  - erosion vs. tissue incorporation
  - migration
  - non-inert
  - rejection by immune reaction
  - infection

What graft characteristics influence these events?
Graft Characteristics Influencing Erosion vs. Tissue Incorporation

- Pore size: macro- or micro porous
- Pore depth
- Type of mesh: multi- or mono-filament
- Neovascularization: Amount allowed
- Surface area
- Rigidity
- Elasticity
- Shrinkage
- Encapsulation
- Immune reaction?
- Wicking of fluids and bacteria
- Surface character
- Degradation
- Toxic polypropylene compounds
- Weight per unit area
- Brittleness
- Oxidation
- Individual patient responses: high or low responder
- Surgical technique
Mileau For Graft Insertion

- Transvaginal placement through a “clean/contaminated” area
- It is impossible to avoid bacterial contamination even with antibiotics used intravenously, by irrigation or by graft soaks
- Studies have shown equal effectiveness of parenteral vs. topical antibiotics

“The Race For The Mesh Surface”

- Once inserted the race begins between the host defenses and the bacteria
- If the bacteria win, the graft is irreversibly contaminated
- Bacteria encase themselves in a slime which frustrates host defenses
- Bacteria have been found on mesh surfaces 6 years after insertion

Gristina AG. Science 1987;237:1588-95
What Influences Amount of Bacterial Contamination?

- The greater the surface area the greater the amount of bacterial attachment
- Multifilament mesh has a 205% increase of surface area compared to a monofilament mesh
- Bacteria can still be harbored in the <10µ interstices of monofilament mesh even though it has a greater degree of neovascularization
- Bacteria 1µ, WBC 9-15µ, macrophages 16-20µ

Polypropylene Wicking

- Fluids and bacteria wick along its surface
- The greater the surface area, the greater the wicking
- Like the Dalkon Shield IUD
- Starts during insertion
- May occur after erosion, particularly when the mesh encapsulates to contaminate it throughout its length
- Accelerated by surface roughness

Is Polypropylene Inert?
Polypropylene Surface Changes

Smooth pre-implantation surface

Where is all this peeled polypropylene going?

Polypropylene Degradation Known Since 1986
Degradation of In Vivo Polypropylene with Free Fragments

- Degradation occurs by oxidation
- A large surface area incites more inflammation
- This results in more oxidation since more macrophages are present
- Macrophages secrete hydrogen peroxide and hypochlorous acid to oxidize the mesh
- Mesh become brittle
- Can polypropylene be completely degraded?
- Where does it go?
- Does it incite a true immune reaction resulting in erosion by actual rejection of the mesh?

Rate of Vaginal Mesh Degradation

- Low weight: 21%
- High weight: 48%
- Non-knitted, Non woven
  - ObTape: 100%
- Multifilament
  - IVS: 75%
- Polyethylene Terephthalate: 0%

What Influences Erosion?

- Quiescent infection become active
- Rigidity and degree of elasticity
- A non-incorporated rigid multifilament microporous mesh fixed in tissue at both ends (TOT) cannot move with the patient’s normal physical activities
- Since the capsule can move, mechanical erosion can occur as the fixed mesh irritates the capsule
- Once erosion occurs bacteria can be wicked into the unincorporated mesh

Other Factors Influencing Erosion

- Hypoestrogenism is assumed to be a factor, but there is no evidence in the literature to support this
- A rabbit study could not demonstrate statistical significance in the occurrence of erosion based on estrogen status
- If the vaginal walls are thinned or actually penetrated during insertion, erosion may occur – especially the fornices during TOT procedures

Other Complications: 
Mesh Contracture, Pelvic Pain And Dyspareunia

- It has been know since 1997 that mesh contracts at least 20% in 10 months
- In 1998 contracture of 30-50% was found at 4 weeks
- A recent study reported 10% per year with an 85% contracture at 8 years
- The tubular vagina constricts and shortens causing dyspareunia
- Nerve fibers are entrapped in the shrinking fibrous tissue causing pain
- Neuromas may form

Mesh Contracture And Pain

- The central body of the large mesh contracts putting tension on the mesh arms anchored in tissue.
- This creates pain and vaginal contracture.

What Causes Mesh Contracture?

- Larger mesh volumes cause greater inflammatory reactions
- More fibrous tissue is produced which continues with relentless non-modifiable contracture over time
- One author recently commented that “it is the gift that keeps on giving” for which there is no cure
- Mesh removal is fraught with many hazards and total removal may require many surgical procedures
- Some have culminated in neo-vaginas

Individual Patient Responses to Mesh Insertion

- Each individual is unique
- Low responders will experience minimal adverse events
- High responders develop more than usual responses
- It is not possible to categorize individual patients at this time
- High tumor necrosis factor??
FDA Mesh Complications
MAUDE Data Base – [www.fda.gov](http://www.fda.gov)

ProteGen™ recalled and FDA agreed based on 34 patients without knowledge of the denominator

<table>
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<tr>
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<th>TVT</th>
<th>ObTape</th>
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<tr>
<td>Fistula</td>
<td>*&lt;1%</td>
<td>0</td>
<td>0</td>
<td>**6%</td>
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<tr>
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<td>1%</td>
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<tr>
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<td>67%</td>
<td>54%</td>
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<td>Pain</td>
<td>&lt;1%</td>
<td>1%</td>
<td>19%</td>
<td>61%</td>
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*Urethral, **Ureteral
FDA MAUDE Data Base - Apogee/Perigee

ProteGen™ recalled and FDA agreed based on 34 patients without knowledge of the denominator

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<tr>
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<td>Vaginal Erosion</td>
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<tr>
<td>Pain</td>
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<td>Dyspareunia</td>
<td>20%</td>
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<tr>
<td>“Concrete”</td>
<td>4%</td>
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49 hospitalizations required for complications
Fiscal and Other Problems for Physicians

- Without data = experimental
- Experimental procedures
  - No health care insurance payment
  - Return of payment demand
  - No malpractice coverage
- Aetna insurance company requires controlled clinical trials in peer-reviewed literature to be non-experimental
- Other than possibly the TVT, is such information available?
Medico-legal Concerns

If you get sued for malpractice what will be read to you in the courtroom---
ACOG Ethical Guidelines

- “Without an adequate evidence base, practitioners cannot determine whether an innovative technique is the most safe and effective method for treating a patient”
- “Without adequate data on the risks and benefits of new treatments, patients are unable to provide a true informed consent”

Despite lack of risk-benefit information, many new techniques and products are being incorporated rapidly into clinical practice, even while continuous modifications are taking place in an attempt to reduce complications.
ACOG Practice Bulletin
Pelvic Organ Prolapse—Feb 2007

- Given the limited data and frequent changes in the marketed products......the procedures should be considered experimental.....patients should consent with that understanding.
- This practice bulletin was withdrawn and was reprinted in September ’07
- Given the limited data and frequent changes in the marketed products......patients should consent knowing the lack of long term data.
Editorial

Marketed vaginal mesh kits: rampant experimentation or improved quality of care?

Nygaard I. *Int Urogynecol J* 2007;18:483-484
FDA Public Health Notification:
October 21, 2008

Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Incontinence

http://www.fda.gov/cdrh/safety/102008-surgicalmesh.html
FDA Recommendations

- Physicians should:
  - Obtain specialized training for each mesh placement technique, and be aware of its risks.
  - Be vigilant for adverse events.
  - Watch for complication of the placement tools (bowel, bladder, vessels).
  - Tell patients that placement is permanent and that complications may not be treatable.
  - Tell patients about QoL complications (pain, vaginal scarring, dyspareunia).
  - Provide written copy of patient labeling from the mesh.
FDA Recommendations

- Physicians should: “...for each mesh”...“be aware of its risks.”
- The only source of risk information is the manufacturer
- This requires evidence based clinical trials
- Will the manufacturers do what is necessary to provide this information??
FDA Information for Patients

- 8 questions are given for the patient to ask the physician, including:
  - Pros and cons of using mesh
  - Can repair be done without mesh?
  - What’s your experience:
    - With this mesh?
    - In dealing with complications?
  - Can the mesh be removed for complications?
Future Decision Making

- Given the lack of evidence based medicine for effectiveness and adverse events:

- For a female surgeon: would you want this procedure done on you?

- For a male surgeon: would you want this procedure done on your mother, wife or sister?
Are we guessing about the effectiveness and safety of meshes??
Risk Factors for Mesh Complications
What Was Known When?

- 1981: Pore size effects fibroblastic in-growth (dogs)
- 1986: Polypropylene degrades in humans
- 1997: Pore size further described
- 1990’s: Mesh shrinkage
- 2002: Mesh surface area related to complications
- 2003: Stiffness of the mesh influences erosion
- Why haven’t manufacturers developed meshes to take these factors into account?

The Path to Erosion and Other Mesh Complications

↑

High Responder
↑

Mesh Insertion → Contaminated Vagina
↑

The Race for the Mesh Surface

↓

Monofilament

Large pore

Low Weight

Smooth Surface

Small Surface area

↓

Host Defenses Win

↓

Acute Inflammatory Reaction → Immune Response

Multifilament

Small Pore

High Weight

Rough Surface

Large Surface Area

↓

Bacteria Win
Chronic Inflammatory Reaction

↓

Macrophages Secrete Acidic Compounds

↓

Oxidation

↓

Degradation → Brittleness

↓

→ Surface area

↓

→ Roughness

↓

Absorbed Polypropylene

↓

Immune Response??

↓

Enhanced Inflammatory True Rejection??

↓

Mesh Shrinkage
Continued Enhanced Inflammatory Reaction

↓

Erosion ← ← ← ← Infection

Surgeon:
Thin or Punctured Vagina

↓

Wicking

↓

Total Mesh Infection
The Ideal Mesh

- Non-reactive in tissue
- Repels bacterial adherence
- No degradation post implantation
- No antigenicity
- No scar tissue stimulation
- No shrinkage over time
- No erosion or migration
Proposed Simple Mesh

No interstices

No place for bacteria to hide

But, it still has a surface area for bacterial adherence

Welded joints

Mono-filament

Flexible

Light weight
Proposed Simple Mesh
Let’s continue to look for the perfect mesh, but---
Let’s discover it using evidence based medicine
Otherwise, how will we know when we have found it?
Don’t Confuse Medical Marketing with Science!

 Require Evidence Based Medicine!
Thank You!!