Polypropylene Mesh in Vaginal Surgery
Risk Analysis & Alternatives

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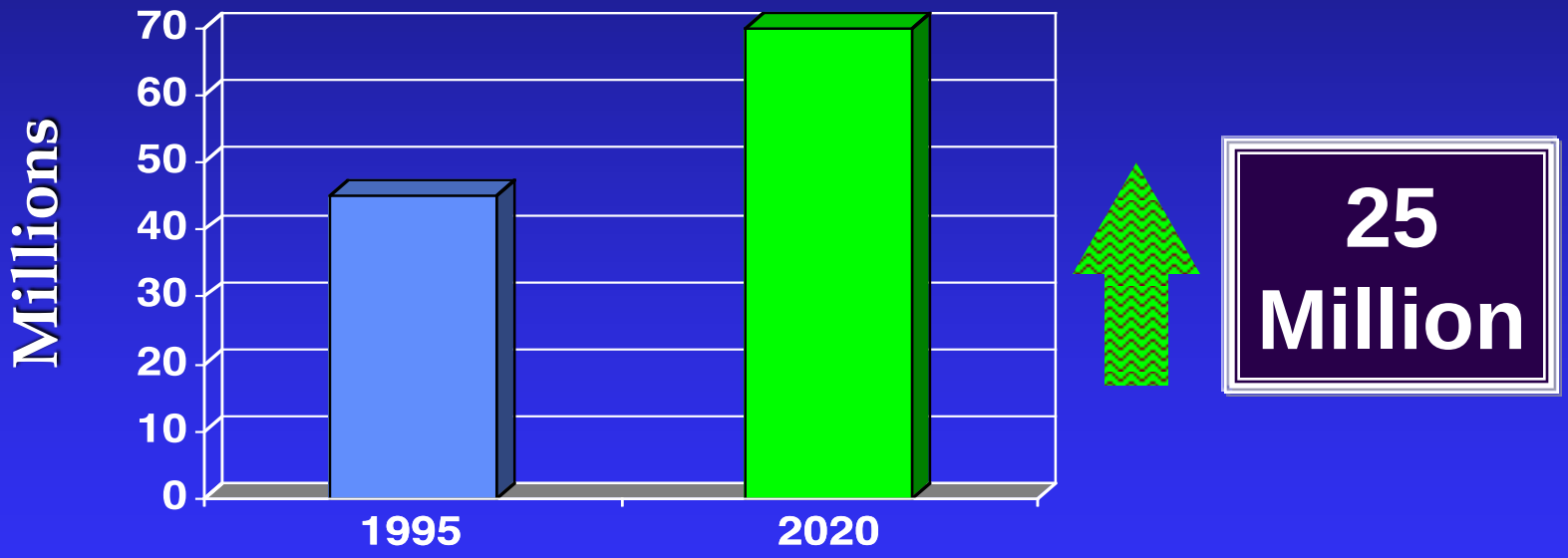
DEMOGRAPHICS

- Average age of menopause US is 50 yrs. & life expectancy of women is 80 yrs thus,
- Women live greater than 1/3 of their lives in the postmenopausal years

- U.S. Census Data 2006
  - 300 million people in the US
    - 152 million women
      - 60 million women 45 yrs old and greater
        - 20% of the population

NET GROWTH IN NUMBER OF WOMEN 45 Y/O & OVER (1995-2020)



*US Bureau of the Census 1994

DEMOGRAPHICS

- Since the majority of incontinence & prolapse occurs in the late & post-reproductive age group, pelvic floor defects will continue to affect large numbers of women well into the future

LIFETIME RISK OF UNDERGOING A SINGLE OPERATION FOR PROLAPSE OR URINARY INCONTINENCE

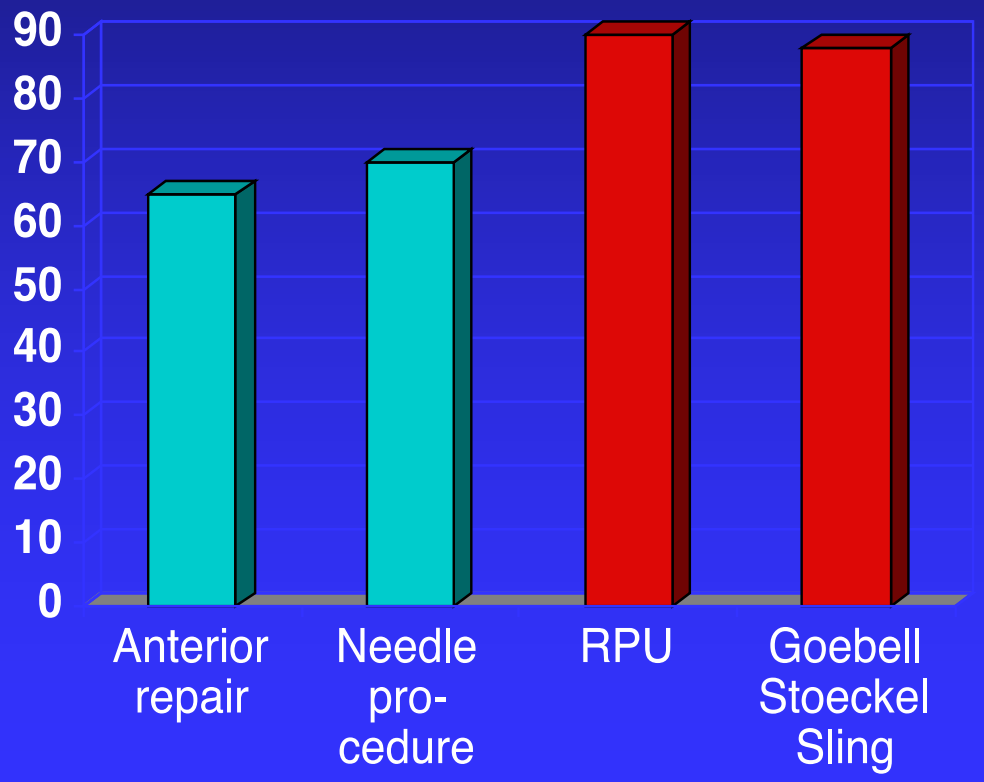
- Olsen et al *Obstet Gynecol* 1997;89:501-6
- Reviewed literature
  - 50% of parous women have prolapse
- Studied women age 20 & up
  - lifetime risk of single operation by 80 yrs. 11.1%
  - risk of reoperation = 29.2%

SURGERIES FOR SUI

Almost 200 procedures have been described

- Kelly plication
- Needle suspension procedures
- Retropubic urethropexy:
  - Open, scope & robotic
- Sling operations:
  - Old & new
- Periurethral injections
- Artificial sphincter
- Urinary diversion

10 YEAR CURE RATES FOR VARIOUS PROCEDURES (%)



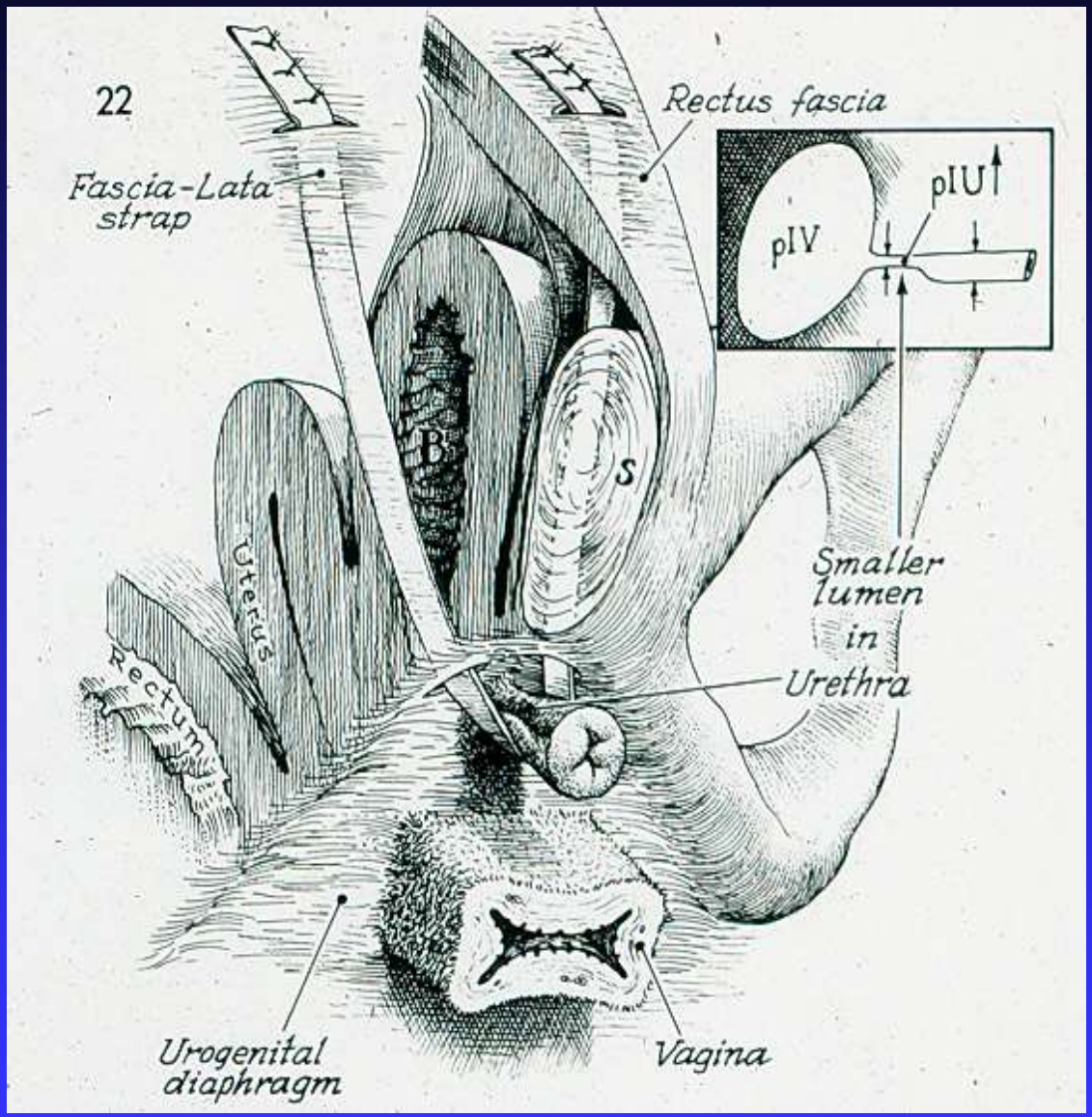
SOME GENERAL COMMENTS ON SLING PROCEDURES

GOEBELL-FRANKENHEIM-STOECKEL FASCIA LATA SLING PROCEDURE

- First described in 1907
- Indicated for type III SUI(aka ISD)
  - Characterized by:
    - Absence of urethral hypermobility
    - Low UPP (<20 cm H20)
    - Valsalva leak point pressure <60 cm H2O
    - Often seen in pts. with hx previous surgery

SOME GENERAL COMMENTS ON SLING PROCEDURES

- Slings are:
  - by definition obstructive procedures
  - always done blindly, thus risk of injury to adjacent organs is high
  - have higher complication rates than RPU's


22
Rectus fascia
Fascia-Lata strap
pIV
pIU
B
S
Uterus
Rectum
Smaller lumen in Urethra
Urogenital diaphragm
Vagina

GOEBELL-FRANKENHEIM-STOECKEL FASCIA LATA SLING PROCEDURE

- Pros:
  - >90% success rate
- Cons:
  - Bladder/urethral injuries
  - Urethral obstruction (5-15%)
  - DI

The Fascia Lata Sling Procedure for Treating Recurrent Genuine Stress Incontinence of Urine
Beck, RP et al Obstet Gynecol 72:699, 1988

- 22 yr experience with fascial lata sling
- 170 patients
- Cure rate 92.4%

SLINGS-Last 15 years

- Indications for slings liberalized because:
  - Increase in # of baby boomers reaching menopause w/ SUI
  - Inexpensive plastic materials are readily available
  - Ins companies pushing OP procedures
  - Slings are easy to teach, easy to perform & fast
  - Slings bill out at a high reimbursement rate

Polypropylene

What is Polypropylene?

- Thermoplastic synthetic polymer made from the monomer propylene

Polypropylene

- Applications:
  - Packaging
  - Textiles
  - Plastic parts
  - Reusable containers
  - Indoor/outdoor carpeting
  - Laboratory equipment
  - Loudspeakers
  - Automotive components
  - Medical

What is Propylene?*

*Dow Product Safety Assessment

- Hydrocarbon monomer produced from fossil fuels (petroleum, natural gas and coal)
- A colorless, highly flammable gas produced as a byproduct of oil refining & natural gas processing
- During oil refining, propylene is produced as a result of the cracking of hydrocarbon molecules
- A major industrial chemical intermediate that serves as a building block for an array of chemical and plastic products including polypropylene

TENSION FREE VAGINAL TAPE TVT

- The most popular of the current sling procedures because:
  - Outpatient procedure
  - Easy to do & short procedure
  - Tolerable success rate
  - Aggressive marketing by industry
- Problem
  - TVT is a sling & thus has a higher complication rate than MMK/Burch
  - It carries the risks of polypropylene mesh

PUBLISHED TVT COMPLICATIONS

- Deaths
- Major vascular injury w/ hemorrhage
- Visceral injuries-bladder/bowel
- Urethral obstruction
- Detrusor instability
- Pain/dyspareunia
- Permanent irreversible synthetic material related
  - Infection, erosion, fistula

Grafting in Gyn Surgery-General Theory

- Why use graft?
  - Ostensibly
    - Strengthen surgical repair
    - Improve success rate
    - Improve function, anatomy & symptoms
  - Requirements
    - Has to be safe
    - Has to be inert
    - Has to be effective
    - Low complication rate
    - SHOULD HAVE AN ADEQUATE EXIT STRATEGY-Should be reversible
- THE BENEFITS HAVE TO OUTWEIGH THE RISKS

Grafts

- Biologic
  - Autologous-self
  - Allograft-same species
  - Xenograft-different species
- Synthetic
  - Permanent v. absorbable
  - Material-polypropyene, gortex, etc.
  - Braided or monofilament
  - Architecture (woven or knitted)
  - Pore size
  - Density
  - Stiffness

Biology of Prosthetic Implant

- Day 3
  - Inflammation
    - Exudative, then cellular
- Day 10
  - Fibroblastic ingrowth
- Week 6
  - Complete ingrowth
- Prosthetic strength doubles from week 3 to 12
- Ongoing remodeling of implant persists beyond 12 months

* Petit J, J Chir, 1974
* Adloff M, Chirugie 1976

Emphasis
Transvaginal Polypropylene

- The most common mesh used today
- Amid classification type I
  - Macroporous
    - Pore size > 75 microns allows for
      - High collagen deposition
      - High capillary penetration
      - High attachment strength
  - Theoretically resistant to infection
      - Macrophages enter larger pores

Known Issues Unique to Polypropylene Mesh

- Mesh shrinkage
- Mesh Erosion
  - Early vs Late
- Mesh Infection
- Dyspareunia
- Chronic Pelvic Pain
- Mesh Degradation

FASCIA LATA SLING PROCEDURE

**Female Urology* Blaivas 1994

- Synthetic material should not be used because risk of:
  - Chronic foreign-body reaction
  - Infection in space of Retzius
  - May erode through urethra or vagina or cause fistula (20% risk*)

Mesh Shrinkage

- Polypropylene “cross-hatched” mesh
  - 2D sheets shrink 20% in surface area*
  - 3D plugs shrink 75% in total volume
- Shrinkage caused by fibroblast contraction of scar plate around mesh
- Results in more contraction on adjacent tissue than desired

*Amid PK, Hernia 1997

Differences in polypropylene shrinkage depending on mesh position in an experimental study

- Garcia-Urena, MA, et al Am J Surg, 2007 Apr;193(4):538-42.
  - Polypropylene mesh (5x3.5 cm) implanted into 15 rabbits
  - 5 animals each were euthanized at days 30, 60 and 90
  - Mesh areas calculated
  - Mesh areas reduced by 25.92%, 28.67% and 29.02% respectively
- "These observations support the theory of PP mesh shrinkage as a consequence of the incorporation of the biomaterial to the scarring tissue"

Mesh Complications Review Shah & Badlani IJU, 2012

- Retraction of tissues surrounding the mesh is usual with a reduction in the size of the mesh
- Average shrinkage is 25-30%
- Shrinkage may reach 40% of the initial surface of the implant after surgery

Klinge U, Klosterhalfen B, et al.
Shrinking of polypropylene mesh in vivo: an experimental study in dogs. Eur J Surg. 1998 Dec;164(12):965-9

- 30-50% shrinkage rate with polypropylene mesh

Effects of Mesh Weight

- Heavier (g/m2) mesh associated with
  - Greater and more prolonged inflammation
  - Greater scar plating
  - Less elasticity
  - Ongoing inflammation & remodeling at 1 year
- Some suggestion that surface area, not just density, is responsible.
  - This is why POP kits are more problematic than slings, there's more mesh

Mesh Erosion

Risk Factors for Mesh Erosion

- Age > 70
- Smoking
- Concomitant hysterectomy
- Stage of prolapse > 2
- Estrogen deficiency
- Dosage of mesh
- Infection

RCT's Mesh Cure & Erosions for Anterior POP

- Iglesia 2010 Mesh Cure 40.6% Erosion 15.6%
- Withagen 2011 Mesh Cure 90.4 % Erosion 16.9%
- Nieminen 2010 Mesh Cure 87% Erosion 19%

Mesh related infections after POP repair surgery *Eur J Obstet Gynecol Peprod Biol* Falagas, et al 2007

- Incidence of mesh erosion including exposure, extrusion and perforation initially described in the literature varies widely from as high as 33%

Mesh Erosion From ASCP/TAH

- Abdominal Sacral Hysteropexy: a pilot study comparing sacral hysteropexy to sacral colpopexy with hysterectomy.
  - Cvach K, Geoffrion R, Cundiff GW. Female Pelvic Med Reconstr Surg, 2012 Sep-Oct; 18(5):286-90
- Graft erosion occurred in 33% of patients undergoing TAH with concurrent ASCP
- The problem arises from implantation of synthetic mesh through or next to a contaminated wound

Mesh Complications-2012

Reported Complication	Range Based on Case Series (%)	Range Based on Randomized Controlled Trials (%)
Mesh erosion (exposure)	1–18.8	5–19
Buttock, groin, or pelvic pain	2.9–18.3	0–10
De novo dyspareunia	2.2–15	8–27.8
Reoperation*	1.3–7.6	3.2–22

*Does not include reoperation for stress urinary incontinence. FEMALE PELVIC MEDICINE & RECONSTRUCTIVE SURGERY

- **Vaginal Placement of Synthetic Mesh for Pelvic Organ Prolapse**
- Committee on Gynecologic Practice
- Female Pelvic Medicine & Reconstructive Surgery. 18(1):5-9, January/February 2012.

Adverse Events over Two Years after Retropubic or Transobturator Midurethral Sling Surgery: Findings from the Trial of Midurethral Sling (TOMUS) Study

Am J Obstet Gynecol. 2011 November; 205(5): 498.e1–498.e6.

4.7% erosion rate with TVT

As an aside, TOMUS also noted:

42% adverse event rate

20% serious adverse event rate

Tseng, LH, et al Int Urogyn J (2005) 16: 230-235 Randomized comparison of the suprapubic arc sling procedure vs TVT for SUI

- 19.4 % erosion rate with TVT
  - "Rejection of tape"
  - "Protrusion of tape edge"
- 29.1% erosion rate with TVT
  - "Defective vaginal wound healing"

Pathologic evaluation of explanted vaginal mesh: interdisciplinary experience from a referral center

Smith, TM, Delancey, JO et al Female Pelvic Med Reconstr Surg. 2013 Jul-Aug;19(4):238-41

- Review of 1 institutions experience w/ path findings of explanted vaginal mesh over a 2 year period
- 102 explants reviewed
- Indications for removal
  - 42% for erosion
  - 28 % for pain
  - Urinary retention 6%
  - Infection 3%
  - No history provided 25%

Pathologic evaluation of explanted vaginal mesh: interdisciplinary experience from a referral center

Smith, TM, Delancey, JO et al Female Pelvic Med Reconstr Surg. 2013 Jul-Aug;19(4):238-41

- Their conclusions:
- Mesh/sling complications are common
  - 102 removal in 2 years at one institution
- Erosion is common
  - 42% of all explants

TOT COMPARED WITH TVT FOR STRESS INCONTINENCE-A RCT

Ross, S et al Ob/Gyn, Vol. 114, No. 6, Dec. 2009 pp. 1287-1294

- Randomized 199 women (50-51y/o) to TOT v TVT & evaluated at 12 mo
- 81% TOT v 77% TVT cured
- On VE tape was palpable in 80% TOT v 27% TVT
- Groin pain felt during VE in 15% TOT v 6% TVT
- Authors Conclusions: The presence of palpable tape, particularly in the TOT group is concerning. Longer f/u needed to determine whether this leads to extrusion over time

Graft-related complications and biaxial tensiometry following experimental vaginal implantation of flat mesh of variable dimensions

Manodoro, S et al BJOG. 2013 Jan;120(2):244-50

- Gynemesh M implanted into vagina of 20 ewes and sacrificed at 60 & 90 days
- 5 x 5 cm mesh implants led to exposures in 30% of cases
- Average contraction rate was 52% +/- 14%
- 3.5 x 3.5 cm mesh implants did not erode but contraction rate was 25% +/-26.3%

Comparison of polypropylene mesh and porcine-derived, cross-linked urinary bladder matrix materials implanted in the rabbit vagina and abdomen

- Fan X, et al; Int Urogynecol J. Nov 29, 2013
- Forty rabbits implanted with PP mesh (n = 20) or cUBM (n = 20) in the vagina & abdomen. Grafts harvested 12 weeks later & processed for histology & biomechanical testing.
- **Vaginal PP erosion rate was 67 %, whereas abdominal PP and cUBM showed no erosion.**
- All patches adhered to vaginal mucosa and shrank to varying degrees, especially PP grafts.

Overall Reported Sling Erosion Rates In Humans

4.7% - 19.4% (29.1%)

Mesh Infection

NORMAL SKIN FLORA

- Staphylococcus epidermidis
- Staphylococcus aureus
- Other Staphylococcus species
- Streptococcus species

NORMAL VAGINAL FLORA

Lactobacillus
Bacteroides
Peptococcus
Peptostreptococcus
Gardnerella
E. coli
Streptococcal
Staphylococcus
Mycoplasmas
Ureaplasma
Enterobacteriaceae
Candida
Mobiluncus
Acinetobacter

ACS-classification of operative wounds based on degree of microbial contamination (Berard F, Gandon J, *Ann Surg* 1964)

- Clean-Elective, not emergency, non-traumatic, primarily closed; no acute inflammation; no break in technique; respiratory, gastrointestinal, biliary and genitourinary tracts not entered.
- Clean-contaminated-Urgent or emergency case that is otherwise clean; elective opening of respiratory, gastrointestinal, biliary or genitourinary tract with minimal spillage (e.g. appendectomy) not encountering infected urine or bile; minor technique break.
- Contaminated-Non-purulent inflammation; gross spillage from gastrointestinal tract; entry into biliary or genitourinary tract in the presence of infected bile or urine; major break in technique; penetrating trauma <4 hours old; chronic open wounds to be grafted or covered.
- Dirty-Purulent inflammation (e.g. abscess); preoperative perforation of respiratory, gastrointestinal, biliary or genitourinary tract; penetrating trauma >4 hours old.

- **Rate of infection (**Cruse and Foord, 1980/1992) 1-2% clean, 6-9% clean-contaminated, 13-20% contaminated & 40% dirty

Mesh Infection
Mesh Complications: Review
Shah & Badlani IJU, 2012

- Incidence of infection 0-8%
- Clinical presentation
  - Non specific pelvic pain
  - Persistent vaginal discharge or bleeding
  - Dyspareunia
  - Urinary/fecal incontinence
  - Induration of vaginal incision
  - Vaginal granulation
  - Draining sinus tracts
  - Graft erosion

Bacterial Colonization of Polypropylene Vaginal Mesh
Vollebregt, et al Int Urogyn, 2009

- Culture swabs of core mesh taken during surgical implantation of vaginal mesh
- 67 implants cultured
- 56 (**83.6%**) implants cultured positive for vaginal bacteria
- Conclusions: "Colonization of vaginally implanted mesh occurs frequently"

Bacteriological analysis of meshes removed for complications after SUI & prolapse surgery, Boulnager, et al *Int Urogynecol J*, 2008

- 16 mesh systems removed
  - 62% for erosion
- Cultures performed
- Bacterial contamination found in **all** meshes

Dyspareunia & Chronic Pelvic Pain In Patients Undergoing Sling and Mesh Surgery

Dyspareunia*

- Up to 24% incidence with TOT
- Pts. undergoing POP surgery 6.2%-24.4%
- Causes:
  - Mesh erosion
  - Mesh infection
  - Mesh shrinkage/contraction
  - Extensive vaginal scarring & fibrosis

*Mesh Complications: Review Shah & Badlani IJU, 2012

Comparison of Dyspareunia Between TVT v Burch Patients

- Oktay Demirkesen, et al: International Braz J Urol, Vol 32 (2):214-219, March-April, 2008
- Evaluated sexual satisfaction rates following TVT and Burch
  - 23% of TVT group expressed neg. changes
  - 9% of Burch group expressed neg. changes
  - Majority suffered from dyspareunia

Urinary complications and sexual function after the TVT procedure

Mazouni, C et al; Acta Obstetricia et Gynecologica Scandinavica, Vol. 83, Issue 10, pages 955-961, Oct 2004

- 71 pts. Evaluated before and after TVT
- 20% reported impaired sexual function after surgery including:
  - 14.5% with dyspareunia
  - 5.4 % with loss of libido

Vaginal Contractility After Mesh

- Deterioration in Biomechanical Properties of the Vagina Following Implantation of a High-Stiffness Prolapse Mesh. Feola, A et al BJOG. 2013 Jan;120(2):224-32

- Implanted Gynemesh PS (Ethicon), SmartMesh (Coloplast) & UltraPro (Ethicon) polypropylene mesh systems into vaginas of 45 rhesus monkeys
- Mesh & vagina excised & studied 3 months later
- Vaginal contractility decreased by 80% with Gynemesh PS, 48% after SmartMesh & 68% after UltraPro

Vaginal degeneration following implantation of synthetic mesh with increased stiffness

Liang, R et al BJOG 2013 Jan;120(2):233-43

- 50 rhesus monkeys implanted with Gynemesh PS or UltraPro in vagina
- 12 control animals without mesh
- Magee-Womens Research Institute at U of Pitt
- Mesh-vagina removed and studied after 3 months

Vaginal degeneration following implantation of synthetic mesh with increased stiffness

Liang, R et al BJOG 2013 Jan;120(2):233-43

- Results
  - Gynemesh PS caused
    - Substantial thinning of the vagina (p=0.02)
    - Increased apoptosis (process of programmed cell death) in the area of the mesh
    - 20% & 43% decreased collagen and elastin content
    - Increased collagenase activity(135% p=0.01)
    - GAG (a marker of tissue injury) was highest w/ Gynemesh PS compared w/ control & other meshes
- Gynemesh PS induced a maladaptive response consistent with vaginal degeneration

Evaluation and Treatment of Dyspareunia

Steege, John F MD; Zolnoun, Denniz MD, MPH
Obstetrics & Gynecology:May 2009-Vol. 113-Issue 5-pp 1124-1136

- Of the many studies reporting on suburethral slings:
  - "Most do not adequately evaluate dyspareunia"…..
  - but, those that do inquire report denovo dyspareunia occuring in 8-69% of pts. (average 15-30%)

Polypropylene Vaginal Mesh Grafts in Gynecology

Ostergard, D, Ob & Gyn, Oct. 2010-Vol. 116-Issue 4-pp 962-966

- "In 1998, Klinge reported shrinkage of 30% to 50% after 4 weeks. Because the vagina is a tubular structure, a decreased caliber & shortening are the inevitable results. Dyspareunia can be explained by such mesh shrinkage, as well as by tension on mesh arms with neuroma formation. Because the mesh is anchored in tissue, its shrinkage will put more & more tension on the anchoring tissue, with resulting pain. No mesh seems to be immune from this process."

Polypropylene Vaginal Mesh Grafts in Gynecology

Ostergard, D, Ob & Gyn, Oct. 2010-Vol. 116-Issue 4-pp 962-966

- "The real tragedy is that the mesh is so firmly incorporated into tissue that its total removal, if indicated, is literally impossible. Unfortunately, this fibrous tissue will continue to contract regardless of what the surgeon trying to remove the mesh is able to do. The more surgery, the more scar tissue that will form."

In Short

- The damage done to the vagina from trans-vaginal polypropylene is:
  - **Severe**
  - **Permanent**
  - **Progressive**
  - **Irreversible**

Chronic Pelvic Pain*

- Groin & thigh pain in 40% TOT pts.
- In POP surgery, the incidence of chronic pain published is 1.9%-24%
- Causes:
  - Mesh erosion
  - Mesh infection
  - Mesh shrinkage/contraction
  - Extensive vaginal scarring & fibrosis

*Mesh Complications: Review Shah & Badlani IJU, 2012

Trocar Related Injuries

- Bladder
  - Urethra, bladder and ureter
- Bowel
  - Rectum and small bowel
- Blood vessel
  - Iliac, obturator, inferior epigastric and pudendal
- Nerve
  - Obturator, pudendal, iliohypogastric

Bladder Perforation Rate

- Wei JT, et al, A midurethral sling to reduce incontinence after vaginal prolapse repair. N Engl J Med. 2012 Jun 21;366(25):2358-67
- Bladder perforation rate 6.7%

- Andonian, S, et al, Randomized clinical trial comparing SPARC and TVT: one year results. Eur Urol. 2005 Apr;47(4):537-41
- Bladder perforation 24% vs 23% (SPARC vs TVT)

Bladder Perforation

- U.S. experience with TVT procedure for SUI: assessment of safety and tolerability *Tech Urol* 2001 Dec;7(4):261-5. Niemczyk et al
  - 100 pts. with SUI underwent TVT
  - Bladder penetration occurred in 24 (24%)
  - Conclusion "TVT is safe"

Overall Reported Bladder Perforation Rates

6.7% – 24%

Voiding Dysfunction & Urgency After Sling

Reported Complications of TVT Procedures: A Review. Rapoport, D., et al. BCMJ, Vol. 49, No. 9, November 2007, pages 465-524

- Reviewed 31 articles re. TVT complications
- Found:
  - De novo urgency & voiding dysfunction 31.5%
  - Urinary retention 19%

Urinary complications and sexual function after the TVT procedure

Mazouni, C et al; Acta Obstetricia et Gynecologica Scandinavica, Vol. 83, Issue 10, pages 955-961, Oct 2004

- 71 pts. evaluated (with urodynamics and questionnaire) before and after TVT
- Postop findings:
  - Voiding difficulty in 60%
  - Urinary urgency in 47%
  - Sig. outflow obstruction in 34.5%
  - Urinary frequency in 33%

Problems With Synthetic Slings

Urogynecology & Reconstructive Pelvic Surgery 3rd Ed.
Walters & Karram, 2007

- Foreign body inflammatory rxn to mesh results in higher risk of erosion & fistula compared w/ autologous material
- Incidence of voiding disorders 2%-37%
- Incidence of DI 3%-30%
- Erosion 5%
- Sling revision or removal 1.8%-35%

Underreporting of Complications After Sling

Am J Obstet Gynecol. 2014 Feb;210(2):163 **Evaluation and management of complications from synthetic mesh after pelvic reconstructive surgery: a multicenter study.**

Abbott S, Unger CA, Evans JM, Jallad K, Mishra K, Karram MM, Iglesia CB, Rardin CR, Barber MD.

- Physicians who perform mesh procedures may not be aware of the complications their patients experience and these providers may be responsible for future mesh-related complications with no awareness of the existing magnitude of the issue

Am J Obstet Gynecol. 2014 Feb;210(2):163 **Evaluation and management of complications from synthetic mesh after pelvic reconstructive surgery: a multicenter study.**

Abbott S, Unger CA, Evans JM, Jallad K, Mishra K, Karram MM, Iglesia CB, Rardin CR, Barber MD.

- Most of the women who seek management of synthetic mesh complication after POP or SUI surgery have severe complications that require surgical intervention & a significant proportion require >1 surgical procedure

Effect of the Material

- Is polypropylene truly inert?
  - No-If it were, the immune system would not mount a foreign body rxn to it!
    - "Chronic foreign body giant cell rxn"
- Inflammation, oxidation and degradation occurs with polypropylene implants
- What are the effects of the degradation products? **Unknown, nobody's studied it.**

Patel H, Int Urogynecol J (2012) 23:669-679

Polypropylene as a reinforcement in pelvic surgery is not inert: Comparative analysis of 100 explants Clave, et al Int Urogynecol J 2010

- Contrary to the prevailing understanding of polypropylene as an inert material when used in vaginal surgeries, the authors noted that all explants showed evidence of degradation on SEM

Polypropylene as a reinforcement in pelvic surgery is not inert: Comparative analysis of 100 explants Clave, et al Int Urogynecol J 2010

- Mesh damage included
  - Superficial degradation with peeling of the fiber surface, transverse cracks in the implant threads, significant cracks with disintegrated surfaces & partially detached material & superficial & deep flaking
  - Polypropylene implants degraded more in the presence of infection or inflammation (common in vaginal implants)

Chevron Philips

Material Safety Data Sheet

1/28/2004

- MARLEX POLYPROPYLENES (ALL GRADES)
- MEDICAL APPLICATION CAUTION: Do not use this Chevron Phillips Chemical Company LP material in medical applications involving permanent implantation in the human body or permanent contact with internal body fluids or tissues.

Material Safety Data Sheet

SECTION 1 PRODUCT AND COMPANY IDENTIFICATION

MARLEX® POLYPROPYLENES (ALL GRADES)

Product Use: Coatings
Synonyms: PLASTIC
Product Cas No.: MIXTURE

Company Identification:
Chevron Phillips Chemical Company LP
10001 Six Pines Drive
The Woodlands, TX 77380

Product Information:
MSDS Requests: (800) 852-5530
Technical information: (800) 852-5531

24-Hour Emergency Telephone Numbers
HEALTH :CT Emergency Information Center (800) 231-0623 or (510) 231-0623
TRANSPORTATION : North America: CHEMTREC (800) 424-9300 or (703) 527-3887
ASIA: (800) ALERTSGS or (800) 25378747 or +65+6542+9595
EUROPE: BIG +32+14+584545 (phone) or +32+14+583516 (telefax)
SOUTH AMERICA SOS-Cotec inside Brazil: 0800+111+767
Outside Brazil: 55+19+3467+1600

MEDICAL APPLICATION CAUTION: Do not use this Chevron Phillips Chemical Company LP material in medical applications involving permanent implantation in the human body or permanent contact with internal body fluids or tissues.

Do not use this Chevron Phillips Chemical Company LP material in medical applications involving brief or temporary implantation in the human body or contact with internal body fluids or tissues unless the material has been provided directly from Chevron Phillips Chemical Company LP under an agreement which expressly acknowledges the contemplated use.

Chevron Phillips Chemical Company LP makes no representation, promise, express warranty or implied warranty concerning the suitability of this material for use in implantation in the human body or in contact with internal body fluids or tissues.

SECTION 2 COMPOSITION/INFORMATION ON INGREDIENTS

Bloomberg Businessweek June 26, 2013

- Managers at Bard's Davol unit used polypropylene made by Chevron Phillips Chemical Co. to produce vaginal-mesh products after Chevron officially registered a warning that it shouldn't be permanently implanted in people, according to e-mails and documents in a lawsuit over Bard's implants.
- In 2004 and 2007 e-mails filed in federal court in West Virginia, a Davol executive warned colleagues not to tell Chevron Phillips or other resin makers that the company was using the material in medical devices placed in humans.

AR Without Synthetic Mesh

- Gandi 2005, AC success rate 71%
- Meschia 2007, AC success rate 81%
- Hviid 2010, AC success rate 85%
- Randomized trial of 3 techniques of AR (no polypropylene) Chmielewski, et al AJOG 2011
  - 88% success rate

AR vs Transvaginal Mesh

Altman et al. NEJM 2011

- Multi-center RCT
- AR vs Anterior Prolift
- Outcome at 12 mo. POPQ stage 0-1 and absence of bulge sx's

Good News for Mesh Proponents:

- Mesh ↓ objective failure rate 14 v. 49%
- Mesh ↓ subjective failure rate 17 v 28%

AR vs Transvaginal Mesh

Altman et al. NEJM 2011

- Bad News for Mesh Proponents
- AR had less de novo apical & posterior prolapse than mesh 9.5% v. 17.7%
- Mesh had longer OR times & greater blood loss
- Mesh had greater cystotomy rate 3.5 % v. 0.5 %
- Mesh had more postop de novo SUI 12.3% v. 6.3%

AR vs Transvaginal Mesh

Altman et al. NEJM 2011

- Bad News for Mesh Proponents
- Mesh erosion rate 10.4%
- Mesh had higher reoperation rate 10.2% v. 5.8%

Quality of Life

  - "The universally agreed upon most important outcome parameter defining success rate"
  - NO DIFFERENCES BETWEEN MESH AND STANDARD AR

- Conclusions-mesh should not be used

Regarding the Evidence for Use of Synthetic Mesh in the Anterior Compartment

Other studies have corroborated the Altman study and have concluded that there is no benefit of using polypropylene mesh in the anterior compartment

Maher, et al April 30, 2013 Cochrane Summaries: Surgical Management of POP

- Review of 56 published trials including 5954 women
- ASCP better than SSLF
- Transvaginal grafts (biologic and synthetic) reduce risk of prolapse when compared to native tissue repair
- HOWEVER……..

Maher, et al April 30, 2013 Cochrane Summaries: Surgical Management of POP

- Disadvantages of polypropylene mesh include:
  - Longer operating time
  - Greater blood loss
  - Prolapse in other areas of the vagina
  - New onset SUI
  - Mesh erosion rate was 18%
- "there is a lack of evidence to support transvaginal mesh operations used in apical or posterior compartment surgery"

Three-Year Outcomes of Vaginal Mesh for Prolapse-A RCT

Gutman, et al Obstet Gynecol Vol. 122, No. 4, October 2013

- Planned 3 yr f/u of 65 women study that was halted because of 15.6% erosion rate
- **"We found no significant differences in cure rates at 3 years between the mesh and no-mesh groups regardless of the definition used"**
- Mesh group had a greater than 15% risk of mesh exposure

FDA

- In October 2008, FDA issued a warning on higher-than-expected complications reported for use of mesh in transvaginal surgeries
- The FDA warning states: "Over the past three years, the FDA has received over 1,000 reports from nine surgical mesh manufacturers of complications that were associated with surgical mesh devices used to repair POP and SUI…

FDA

- Complications included:
  - erosions through vaginal epithelium
  - infection
  - pain
  - urinary problems
  - recurrence of prolapse and/or incontinence.
  - bowel, bladder, and blood vessel perforation during insertion

FDA

- vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia

FDA

- On July 13, 2011, the FDA stated in a news release:
  - "There are clear risks associated with the transvaginal placement of mesh to treat POP."
  - "The FDA issued a safety communication in 2008 due to increasing concerns about adverse events associated with the transvaginal placement of mesh. Since then, the number of adverse events has continued to climb. From 2008 to 2010, the FDA received 1503 adverse event reports associated with mesh used for POP repair, five times as many as the agency received from 2005 to 2007."

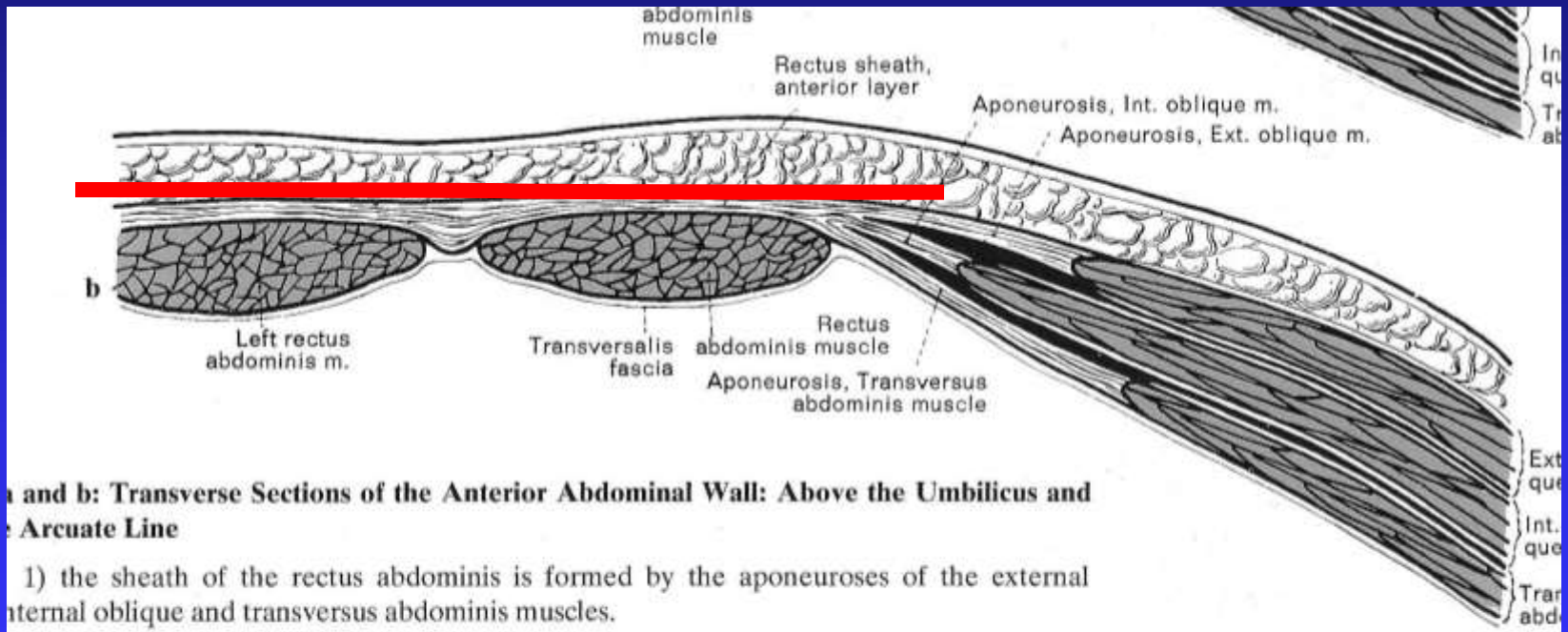
FDA

Surgical mesh for POP was subsequently reclassified from Class II to Class III, requiring premarket and postmarket studies.

- Regrettably, the instructions for use (IFU's) and directions for use (DFU's) published by the sling and mesh manufacturers superficially touch on only some (not all) of the complications described herein and even then in a wholly inadequate manner

What about the argument that using polypropylene mesh in abdominal hernias is ok so therefore it must be ok to use it in the vagina?

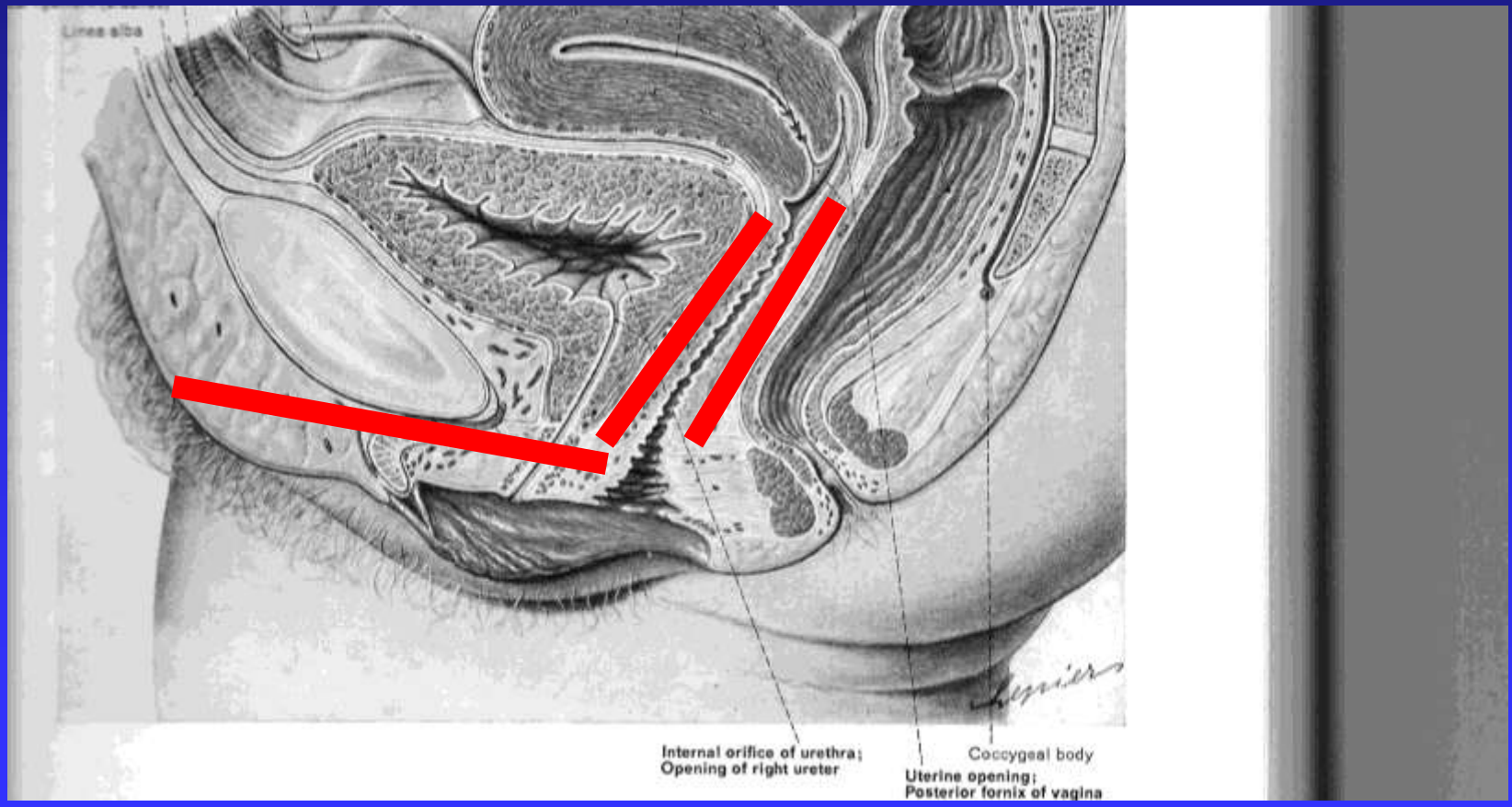
The anatomy, mechanics and biology of implanting a piece of mesh in the abdominal wall…



and b: Transverse Sections of the Anterior Abdominal Wall: Above the Umbilicus and Arcuate Line

1) the sheath of the rectus abdominis is formed by the aponeuroses of the external nternal oblique and transversus abdominis muscles.
upper two-thirds of the sheath encloses the rectus muscle both anteriorly and posteriorly ccomplish this, the internal oblique aponeurosis splits. Part of this aponeurosis joins urosis of the external oblique to form the anterior layer, while the other portion joins the aponeurosis of the transversus to form the posterior layer.
ower one-third of the sheath (b), below the arcuate line, is deficient posteriorly, since the aponeuroses of all three muscles ior to the rectus abdominis muscle.

…is fundamentally different than implanting the same mesh in the vagina



Is There A Conflict of Interest Regarding Mesh Use in The Medical Community?

- AUGS has been a vigorous champion of polypropylene mesh
  - describe mesh as the “gold standard”
- 2011 - AUGS received > $220,000 in industry support
- 2014 - 8 of the 14 AUGS BOD receive industry $$
- 2011 & 2014 - AUGS BOD refused to acknowledge a conflict of interest in their public statements supporting mesh
- Key opinion leaders that promote mesh receive significant industry $$

Misuse Of The Phrase "Gold Standard"

- BMJ. May 14, 2005; 330(7500): 1121. **The gold standard: not a golden standard** Jurgen AHR Claassen
- Between 1995 and 2005 over 10,000 publications have mentioned "gold standard"
- Medline Search 4/8/2014 for "gold standard" showed over 170,000 citations

What is the Gold Standard for SUI Surgery?

- Karram 2012 says its the pubovaginal sling
- TeLinde's Operative Gynecology 2014 says its the Burch
- AUGS 2014 says its the polypropylene sling

- So who's right?
- Nobody, the term is 100% subjective and therefore meaningless

Putting It All Into Perspective

- 1907 Goebell Stoeckel sling introduced
- 1998 TVT launched
- 2001 CPT panel of the AMA added 57287 (removal/revision of sling) to the codebook

- 2004 Mesh for POP launched
- 2006 CPT panel of the AMA added 57295 (removal of mesh) to the codebook

Putting It All Into Perspective

- There is a code to put slings in & there is a code to take slings out
- There is a code to put mesh in & there is a code to take mesh out

- Polypropylene sling & mesh devices are the most common urogynecologic implants to require subsequent removal

In Fact

- If sling revision or removal is necessary in 1.8%-35% of women (as Walters and Karram describe in 2007)

and

- Millions of women currently have implanted slings

then

- Hundreds of thousands (? millions) of women may undergo surgery that was totally preventable

Ulmsten

- 1996 Ulmsten 1st described the TVT for SUI. Subsequently, he was paid $400,000 by Ethicon to publish what would become the landmark study on TVT but payment was contingent on two required findings:
  - The study had to show TVT was effective
  - The study had to show TVT was safe

What's Happening Elsewhere?

- "UCLA surgeons are now performing more sling procedures using the patient's own tissue and bladder neck suspensions using non-absorbable sutures, both of which avoid the use of surgical mesh"

What's Happening Elsewhere?

- On 6/17/14, Scotland's Health Secretary, Alex Neil suspended the use of all transvaginal polypropylene mesh implants (POP and Sling) pending safety audits

Conclusions

- Polypropylene trans-vaginal slings & mesh:
  - Cause numerous serious, permanent & irreversible complications
  - Multiple high risks far outweigh the few benefits
  - Are defective devices/surgical theory
  - There are far safer & effective alternatives
  - Are the single worse defective product ever perpetrated on women

Conclusions

- The risks of polypropylene mesh in prolapse & SUI surgery clearly outweigh the benefits
- There are several superb alternatives to mesh that have a 0% mesh complication rate
- Don’t use trans-vaginal polypropylene mesh in any capacity