Basic Science: Insight into the Pathogenesis and Treatment of Pelvic Organ Prolapse

W22, 29 August 2011 14:00 - 18:00

Start	End	Topic	Speakers
14:00	14:05	Intro	• Harold Drutz
14:05	14:45	Insight into the genetics of pelvic organ prolapse (POP) and factors that promote and degrade extracellular matrix (ECM)	• May Alarab
14:45	15:30	Mechanisms by which maternal birth injury alters the loading environment of the vagina	• Steve Abramowitch
15:30	16:00	Break	All
16:00	16:30	Animal models for pelvic organ prolapse	• Andrew Feola
16:30	17:20	Do biological meshes have a role in prolapse surgery?	• Jan Deprest
17:20	18:00	A functional approach to choosing a synthetic prolapse mesh.	• Pamela Moalli

Aims of course/workshop

This workshop will update and educate participants on the latest research into the pathogenesis and treatment of pelvic organ prolapse. Talks on pathogenesis will cover intrinsic differences in connective tissue remodeling in women with and without prolapse that favours a degradative response in the former and not the latter. In addition, mechanisms by which maternal birth injury alters the loading environment of the vagina and predisposes to prolapse will be explored. Attendees will learn the appropriateness of different animal models to study prolapse. Finally, the host response to the surgical repair of prolapse using biological VS synthetic meshes will be reviewed as well as a functional approach to selecting a mesh product.

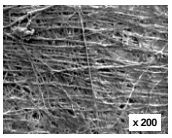
Educational Objectives

This workshop will update those interested in the pathogenesis and surgical repair of prolapse using the best science of the day. Thus, participants will not only be presented with recent data from top labs from around the world but they will also be introduced to state of the art techniques used to answer complicated research questions. Scientific approaches will include biochemical and molecular biology techniques as well as histomorphology, mechanobiology and biomechanics. This workshop will be educational for students and trainees embarking on a basic science career as well as senior scientists. The forum will be informal and interactions with the audience will be encouraged.

Dia 1

“Bio”-meshes

Filip Claerhout
Jan Deprest
Maarten Albersen
Alexander Engels
Yves Ozog
Stefano Manodoro
Pieter Uvin
Dirk De Ridder
Edoardo Mazza*



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**ETH Zurich, Switzerland*

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Dia 2

The problem

- The pandemia of Pelvic Organ Prolapse (POP)
  - Life time risk operation: 11. 1% (Olsen, 1997)
  - Ageing & changed lifestyle: increased expectations
- Surgery is the most common therapy
- Current problems with native tissue repair
  - Recurrence: reoperation rate 30% (Olsen, 1997)
  - Local side effects
- Synthetic implants used to improve results
  - At the expense of local complications

Dia 3

Efficacy and safety of using mesh or grafts in surgery for anterior and/or posterior vaginal wall prolapse: systematic review and meta-analysis

X Jia,[a] C Glazener,[a] G Mowatt,[a] G MacLennan,[a] C Bain,[b] C Fraser,[a] J Burr[a]

	no mesh	Permanent synthetic “mesh”
EFFICACY		
Subjective failure	10,6%	1,8%
Objective failure	28,8%	8,8%
Recurrent surgery	2,4%	1,3%
SAFETY		
Graft related complication	NA	10,2%
Surgery for GRC	NA	6,6%
Pain	??	↑↑

Adapted from BJOG 2008, 115:1350-1361

Dia 4

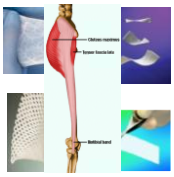
Bio-mesh = grafts (ICS-IUGA 2010)

acellular collagen matrices for augmentation
tolerance rather than rejection
same durability

Autologous grafts
Heterologous grafts
1990s: Xenografts

Non-cross linked
Small intestinal submucosa « SIS »
InteXen (LP)

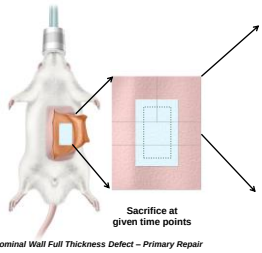
Cross linked
Pelvicol
Pelvisoft



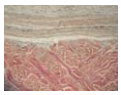
Questions: (1) different host response - (2) strength ?

Dia 5

In vivo animal studies - rodents



Sacrifice at
given time points



Morphometry
Immunohistochemistry
Molecular work

Tensiometry

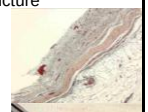
Abdominal Wall Full Thickness Defect – Primary Repair

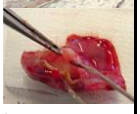
Alponat, et al. 1997, Zheng, 2004, 2005, Konstantinovic, et al 2005

Dia 6

non-cross linked

more open “ECM” structure





layered structure

seroma formation (20%) early on

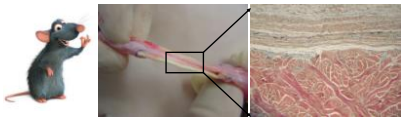
infects (even in rats)

Konstantinovic et al, BJOG 2005

Dia 7

Cross linked collagen matrices

Host response to acellular collagen matrix



Weak inflammatory response
Poor integration
Poor vascularization and collagen deposition
(Cole, 2003; Zheng, 2004-05)

Dia 8

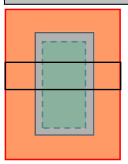
There is a true difference in immune response to xenografts than to synthetic implants

H& E stain

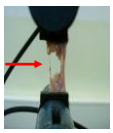
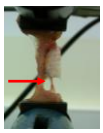
Zheng F, et al. Neurourol Urodyn 2006

Dia 9

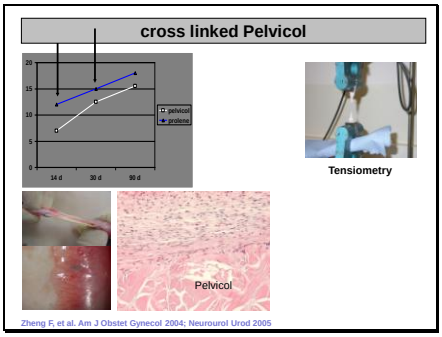
Tensiometry of explant (in vivo)



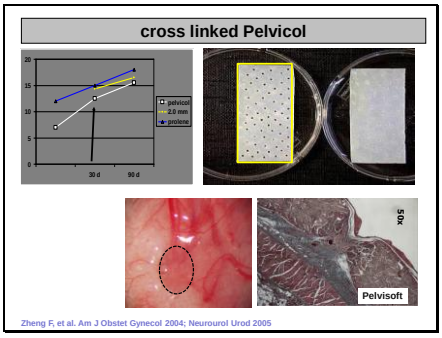
4467 Instron tensiometer
Specimen: 1 x 5 cm
Crosshead speed: 2 cm/ min
Measurement:
maximum load to disrupt (N)
Location of disruption:
in mesh
or at interface

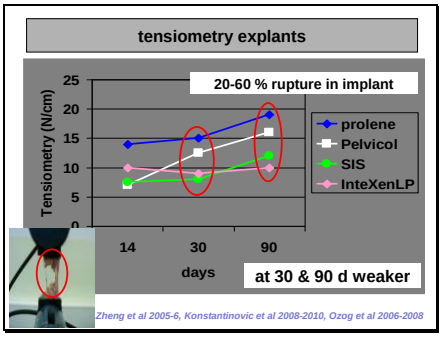

Dia 10



Dia 11

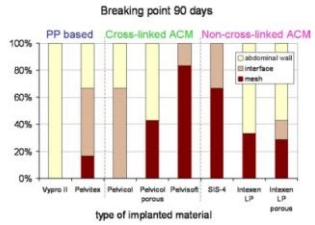


Dia 12



Dia 13

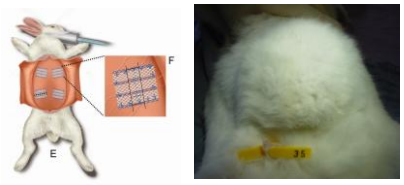
Location of mesh disruption (90 d)



Ozog et al 2006-2008; Konstantinovic et al, Neurourol Urod 2010

Dia 14

In vivo animal studies - rabbits

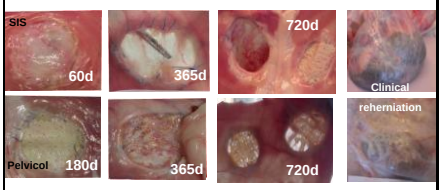


larger size – longer follow up – vaginal surgery is possible

Walter 2003-6, Claerhout 2004, Konstantinovic 2005, Hilger 2006; Huffaker 2008; Pierce 2009; Ozog 2009-10

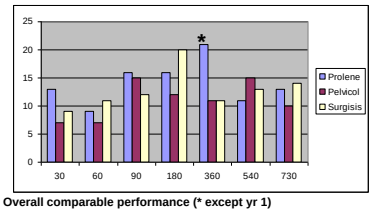
Dia 15

Experimental long term studies



Dia 16

Rabbits - explant strength



- Overall comparable performance (* except yr 1)
- reherniations in both xenograft types
- Degradable grafts tear within the implant
- Occasional loss of elasticity and integrity

Claerhout et al, 2004, AJOG 2008
Trabuco et al, AJOG 2008

Dia 17

long term inflammatory changes

Degradation of the material is an occasional yet unpredictable event
(Ozog, 2009; Claerhout 2005)

Dia 18

Summary Experimental Evaluation

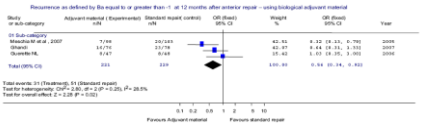
- **induction "different" host response**
- **Non-cross linked materials**
  - **Local effect: swelling, elongation, seroma, infection**
  - **Lower tensiometric strength in some studies**
  - **disrupt more easily within the implant**
- **Cross linked**
  - **Poor true integration with unporous structure**
  - **When porous better ingrowth & stronger**
  - **Occasional degradation and loss of elasticity**

Ideal biomesh not designed yet

Dia 19

Is this clinically relevant ?

- Anterior compartment: better anatomic outcomes with Pelvicol *(Foon, IUGJ 2008)*



- Apical prolapse: xenograft use associated with more failures & reoperations

(Altman Urol 2006; Quiroz, AJOG 2008; Deprest, J Urol 2010; Claerhout, Neurourol Urodyn 2010)

Dia 20

Sacrocolpopexy using xenografts

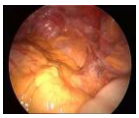
@ 32 months follow up	SIS 21	Pelvicol 29	Polypropylene 100
Objective failure (C≥-1)	22%	19%	3%*

Comparable demographics - no significant functional differences in prolapse, urinary, defecation and sexual function

(Deprest et al, J Urol 2010a)

Dia 21

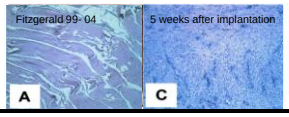
Explant studies



- **Clinically release at vault**
- **Typically most material disappeared, poor interaction**
- **Histology: degradation & presence of foreign body giant cells**

= as in experimental studies

= as with auto/homologous grafts



Deprest J Urol 2010b
Fitzgerald 1999

Aims of course/workshop

Xenografts

To review the biology of xenografts, both cross linked and non-cross linked. The host response in experimental conditions is described as well the current clinical data.

Educational Objectives

Xenografts

To understand the different host response to xenografts as compared to synthetic grafts.
To update the audience on current outcomes with prolapse repair using xenografts.

Recommended reading:

Xenografts: We will refer to the following material from our group:

1. Deprest J, Zheng F, Konstantinovic M, Spelzini F, Claerhout F, Steensma A, Ozog Y, De Ridder D. The biology behind fascial defects and the use of implants in pelvic organ prolapse repair. *Int Urogynecol J Pelvic Floor Dysfunct. 2006 Jun;17 Suppl 1:S16-25.*
2. Claerhout F, Verbist G, Verbeken E, Konstantinovic M, De Ridder D, Deprest J. Fate of collagen-based implants used in pelvic floor surgery: a 2-year follow-up study in a rabbit model. *Am J Obstet Gynecol. 2008 Jan;198(1):94.e1-6.*
3. Claerhout F, De Ridder D, Van Beckevoort D, Coremans G, Veldman J, Lewi P, Deprest J. Sacrocolpopexy using xenogenic acellular collagen in patients at increased risk for graft-related complications. *Neurourol Urodyn. 2009 Sep 3. [Epub ahead of print]*
4. Deprest J, Klosterhalfen B, Schreurs A, Verguts J, De Ridder D, Claerhout F. Clinicopathological Study of Patients Requiring Reintervention After Sacrocolpopexy With Xenogenic Acellular Collagen Grafts. *J Urol. 2010 Apr 16. [Epub ahead of print]*
5. Deprest J, Ridder DD, Roovers JP, Werbrouck E, Coremans G, Claerhout F. Medium Term Outcome of Laparoscopic Sacrocolpopexy With Xenografts Compared to Synthetic Grafts. *J Urol. 2009 Nov;182(5):2362-8.*