WHAT DOES THE RESEARCH SAY REGARDING BIOLOGICAL MATERIALS?

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THE “IDEAL” GRAFT/MESH

• Biocompatible
• Sterile
• Non-carcinogenic
• None-allergenic
• Resistant to mechanical stress
• Affordable
• Available
Biological grafts
- Autologous graft (from the patient’s own body)
  rectus fascia, fascia lata, vaginal mucosa
- Allograft (from post-mortem tissue bank)
  fascia lata, dura mater
- Xenograft (from animals)
  porcine, bovine

Synthetic meshes
- Remodelling; absorbable, non-absorbable, etc.
- Pore size; macroporous, microporous, etc.
- Structure; monofilament, multifilament


THE MINIMUM STANDARDS PRIOR TO LAUNCH AND MARKETING

1. Comprehensive and exact data on the physical properties of the product.
2. Data on the biological properties of the product following implantation from high-quality animal studies.
3. Anatomical studies on cadavers.
4. A well-constructed cohort study.
5. Commitment to a compulsory registration of the first 1,000 consecutive patients after marketing clearance by the appropriate regulatory bodies.

REQUIRES PHYSICAL SPECIFICATIONS OF ALL PRODUCTS

- Nature of the composing polymer (s) and filament (s)
- Resistance of polymer (s) to degradation (permanent or absorbable)
- Weaving type (knitted or woven)
- Filament diameter
- Pore dimensions and density
- Exact dimensions and weight
- Total surface area
- Uniaxial tensile stress-strain plot determining
- Distentional stiffness
- Bending stiffness: flexural rigidity


ANTICIPATED TIME LINE OF THE CURRENT PROPOSAL FOR THE INTRODUCTION OF NOVEL DEVICES INTO THE MARKET

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EVALUATION OF IMPLANT (IN VITRO)

- Mechanical properties
  - tests for surface characterization
  - tests for water absorption
  - tests for matrix degradation
  - tests for strength
- Biocompatibility
  - in vitro cytotoxicity assay
  - cell attachment
- In vitro antimicrobial activity

Implant  Porcine extracellular matrix scaffold

Materials and methods

1. Preparation of
   - small intestinal submucosa
   - urinary bladder matrix
   - acellular dermal matrix
   - cholecyst-derived extracellular matrix
   - acellular pericardium
2. Tests for mechanical properties
3. In vitro cytocompatibility assay

Results

- Different ECM scaffolds have distinct structural differences and all have good biocompatibility.
  

**Implant**

- Autologous rectus fascia (ARF)
- Solvent-dehydrated fascia lata (SD)
- Freeze-dried cadaveric fascia lata (FD)
- Cadaveric dermal graft (DG)

**Main outcome measures**

- Tissue strength analysis
  1. Maximum load to failure
  2. Maximum load per unit width of graft
  3. Stiffness

Solvent-dehydrated cadaveric fascia lata and acellular dermal grafts are indistinguishable from native autologous rectus fascia, in terms of tensile strength and tissue stiffness.

The freeze-dried cadaveric fascia lata allograft, commonly available from tissue banks, is significantly less strong than native fascia or other allograft alternatives.

ANIMAL MODELS IN THE STUDY OF FASCIAL DEFECTS

**Advantages**
- Allow for complex experimental design
- Reduce risks to patients
- Save time and money in understanding the problem

**Limitations**
- Different pelvic floor musculature & birth process
- Difficult to evaluate functional problems and co-factors correctly

**Animal models**

- Mechanical evaluation
- Biocompatibility evaluation
- Failure or local adverse effects anticipation

Rodents; rats, mice
Rabbits
Sheep
Dogs
Rhesus and squirrel monkeys

**DESIGN OF ANIMAL MODELS AND EXPERIMENTS**

One or more standardized full-thickness defects are created in the abdominal wall.

- Implantation of the material
  - Primary suture repair
  - Overlaying the defect

Clinical observation for local and systemic complications.

- Sacrifice

Explant is harvested, divided and conserved for further evaluation.
OUTCOME MEASURES FOR THE EVALUATION OF EXPERIMENTAL EXPLANTS

• Macroscopy; signs of infection, herniation, folding, contraction or migration
• Biomechanical measures; tensile properties, tissue strength
• Microscopy
  - Histology
  - Immunohistochemistry
  - Flow cytometry
  - Molecular techniques
  - Gene expression profiling
**Implant** Polypropylene mesh (MX) 
Porcine small intestine submucosa (SIS)

**Model** 48 adult male Wistar rats

**Main outcome measures**

1. Location and size of re-herniation  
2. Presence of fluid collection, infection, erosion  
3. Presence of adhesions

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**Implants in the SIS group were significantly thicker in the first 14 days, due to fluid accumulation, with a return to baseline thereafter.**

**The MX implants increased less in thickness, but the change persisted.**

**SIS implants induce less dense adhesion than MX.**

### Implant
- Polypropylene mesh (Prolene)
- Porcine dermal collagen (Pelvicol)

### Model
- 64 adult male Wistar rats
  - sacrificed at 7, 14, 30 and 90 days

### Main outcome measures
1. Herniation, infection, rejection
2. Presence of adhesions
3. Thickness

> The Pelvicol group had less extensive and dense adhesions than the Prolene group at all times.


### Implant
- Non-cross-linked InteXen LP
- Cross-linked Pelvicol
  - Acellular collagen matrices (ACMs)

### Model
- 112 adult male Wistar rats
  - 14, 30 and 90 days after defect repair

### Main outcome measures
1. Total area of adhesions
2. Grade score of strongest adhesions
3. Thickness after implantation

> All cross-linked implants showed a gradual and significant decrease in thickness after 14 days.

> Pelvicol implant areas doubled in size at 90 days which was accompanied by structural degradation.

Implant  Porcine dermal collagen implant
- non-porous
- porous of different diameters

Model  36 adult male Wistar rats
30 and 90 days after defect repair

Main outcome measures
1. Herniation
2. Adhesion

- No herniations were seen in any of the animals.
- Intraperitoneal adhesions were mild or minimal.
- There was no difference in density or the area of adhesions between the different groups.

**Implant**  Polypropylene mesh (MX)  
Porcine small intestine submucosa (SIS)

**Model**  48 adult male Wistar rats

**Main outcome measures**

Tensiometry
1. The maximum load required to disrupt the strip
2. Location of breakage (either at the interface or within the implant)

> Explants from the SIS group were weaker than those from the MX group at 30 days.
> Both implant materials have comparable strength at 90 days.

**Implant**  Polypropylene mesh (PP)  
Cross-linked porcine dermis (PS)

**Model**  35 ovariectomized and sham rabbits harvested 9 months later

**Main outcome measures**

Tensile strength  
1. Maximum load to material failure  
2. Graft stiffness  
3. Ultimate tensile strength  
4. Tensile or elastic modulus  
5. Ultimate strain


- PP grafts increased in elasticity and decreased stiffness.  
- Ultimate tensile strength and elastic modulus were lower in PS graft from ovariectomized animals compared with those from animals with intact ovaries.  
- At 9 months after implantation, PS overall was similar in strength to PP, but was twice as stiff as PP and a maximal elongation only half that of PP.

Implant  Polypropylene mesh (Prolene)  Porcine dermal collagen (Pelvicol)
Model  64 adult male Wistar rats  7, 14, 30 and 90 days after implantation
Main outcome measures  Tensile load testing

- Pelvicol explants showed a lower tensile strength than Prolene.
- By 90 days there was no statistical significance anymore in strength of the explants between these two groups.


Implant  Gynemesh  Pelvicol (non-parous, cross-linked)  Pelvisoft (cross-linked)  Surgisis (non-cross-linked)
Model  63 adult Wistar rats  1 and 3 months after hernial repair
Main outcome measures  Tensile strength, stiffness

- No difference in adjusted tensile strength was observed among the groups at 1 and 3 months after implantation.

| **Implant** | Non-cross-linked InteXen LP  
|            | Cross-linked Pelvicol  
|            | Acellular collagen matrices (ACMs) |
| **Model** | 112 adult male Wistar rats  
|            | 14, 30 and 90 days after defect repair |
| **Main outcome measures** | Explant maximum stress over time |

- The tensiometric strength of noncross-linked InteXen LP was higher than that of cross-linked Pelvicol at all time point.
- Higher strength does not necessarily lead to a higher level of force resistance of the implant itself.


| **Implant** | Porcine dermal collagen implant  
|            | - non-porous  
|            | - porous of different diameters |
| **Model** | 36 adult male Wistar rats  
|            | 30 and 90 days after defect repair |
| **Main outcome measures** | Tensile load testing |

➢ There was a trend for higher forces required to disrupt the explant with increasing pore size.
➢ This was only significant at a pore size of 2.0 mm at day 30.

Implant: Polypropylene mesh (MX) 
Porcine small intestine submucosa (SIS)

Model: 48 adult male Wistar rats

Main outcome measures

1. H&E stains 
2. Immunohistochemical staining

- There was a more pronounced inflammatory reaction (foreign body giant, polymorphonuclear and mononuclear cells) in the MX group than the SIS group.
- SIS caused a very mild inflammatory response, confirming the low immunogenicity.

### Implant

**Polypropylene mesh** (Prolene)  
**Porcine dermal collagen** (Pelvicol)

### Model

- 64 adult male Wistar rats
  - sacrificed at 7, 14, 30 and 90 days

### Main outcome measures

1. Histopathology  
2. Immunohistochemistry

- **Prolene animals showed a pronounced inflammatory response.**  
- **Prolene implants induced an intense collagen deposition, with the fibers oriented in a more irregular fashion.**


### Implant

**Porcine dermal collagen implant**  
- non-porous  
- porous of different diameters

### Model

- 36 adult male Wistar rats  
  - 30 and 90 days after defect repair

### Main outcome measures

- Histological scores  
- inflammatory reaction  
- vascularity  
- collagen

- **Modification of Pelvicol with the creation of a porous structure promotes tissue integration, neo-vascularization and collagen deposition.**

### Implant Model

**Implant**  
Polypropylene (Prolene)  
Porcine dermal (Pelvicol)  
Small intestine submucosal collagen (SIS)

**Model**  
35 rabbits  
30, 60, 90, 180, 365, 540 and 720 days

**Main outcome measures**
- Morphological study
- Immunohistochemical study

- **Non-cross-linked SIS is constructively remodelled within 3 months.**
- **Cross-linked Pelvicol may also undergo the fate of degradation at a later stage.**


### Implant Model

**Implant**  
Polypropylene (PP)  
Cross-linked porcine dermis (PS)

**Model**  
45 adult New Zealand white female rabbits  
9 months after implantation

**Main outcome measures**
- 1. Inflammation
- 2. Neovascularization
- 3. Fibroblastic proliferation

- **PP induces a milder, more uniform long-term response than cross-linked PS.**
- **PS elicited a more variable response and degraded by 9 months.**

SUMMARY

• Ideally, the strength and elasticity of biological materials implanted in the vagina should be similar to that of healthy vaginal tissue to provide proper support, enable expansion and minimize erosion.

• Synthetic and biological implants demonstrate different biomechanical properties and foreign body reactions.

• Good animal studies to evaluate the safety and efficacy of implants are needed before introduction in the reconstructive pelvic surgery.