Mesh, still too hot to handle?

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Conflicts of interest

Advisory boards: Astellas, Coloplast, Tepha
Unrestricted research grants: Coloplast, Tepha, AMI, Bard, J&J
Image of mesh surgery is damaged

HAVE YOU BEEN
DIAGNOSED WITH SEVERE INTERNAL INJURIES
BECAUSE OF VAGINAL MESH?

Many women who have had a vaginal mesh implanted in the process of treating pelvic organ prolapse have been exposed to severe injuries internally, as well as urinary issues and other complications.

Transvaginal Mesh Lawsuit

In 2011, the Food and Drug Administration issued a public notice regarding transvaginal mesh to doctors after 2,875 injuries relating to pelvic mesh were reported between 2008 and 2010. Right now, cases are being filed individually and no nationwide transvaginal mesh class action lawsuit has been filed.
Change of mesh procedures over time

Evidence to use mesh

Actual use of mesh
Why does the debate split our field?
The future of native tissue surgery is not promising
The working mechanism of mesh

1. It replaces native tissue that is proven to be weak.
2. It induces new collagen formation.
3. It can correct anatomical defects that can not be corrected by conventional surgery.
4. It increases support by augmentation of the supportive surface.
Without implanting a foreign body; surgical repair mainly depends on weak and damaged connective tissue
Hypothesis 3

Change of infrastructure
Is the fastest way to improve outcome of mesh surgery
Principles of Value-Based Health Care Delivery

- The overarching goal in health care must be value for patients, not access, cost containment, convenience, or customer service.

\[
\text{Value} = \frac{\text{Health outcomes}}{\text{Costs of delivering the outcomes}}
\]

- Outcomes are the health results that matter for a patient’s condition over the care cycle.
- Costs are the total costs of care for a patient’s condition over the care cycle.
Volume and outcome are related to each other
Re-organization of care

• Concentrate complex surgery in a few high-volume centers (the Netherlands: > 20 procedures/year*surgeon)
• Mesh-related complications are treated in centers of excellence
• Infrastructure facilitates early detection and management of adverse events
• 100% assessment of outcome, with the capacity to:
  • Monitor centers and surgeons
  • Follow-the implant
  • Develop shared decision tools
Prospect trial

Mesh, graft, or standard repair for women having primary transvaginal anterior or posterior compartment prolapse surgery: two parallel-group, multicentre, randomised, controlled trials (PROSPECT)

Cathryn MA Glazener, Suzanne Breeman, Andrew Elders, Christine Hemmings, Keith G Cooper, Robert M Freeman, Anthony RB Smith, Fiona Reid, Suzanne Hagen, Isobel Montgomery, Mary Kilonzo, Dwayne Boyers, Alison McDonald, Gladys McPherson, Graeme MacLennan, John Norrie (for the PROSPECT study group) *

Summary
Background The use of transvaginal mesh and biological graft material in prolapse surgery is controversial and has led to a number of enquiries into their safety and efficacy. Existing trials of these augmentations are individually too small to be conclusive. We aimed to compare the outcomes of prolapse repair involving either synthetic mesh inlays or biological grafts against standard surgical repair in women.

Methods We did two pragmatic, parallel-group, multicentre, randomised controlled trials for our study (PROSPECT [PRolapse Surgery: Pragmatic Evaluation and randomised Controlled Trials]) in 35 centres (a mix of secondary and tertiary referral hospitals) in the UK. We recruited women undergoing primary transvaginal anterior or posterior compartment prolapse surgery...
Prospect trial

- 35 hospitals, 65 surgeons
- < 7 meshes per surgeon in this trial
- No clue about “quality of surgery”
  - Learning curve
  - Trans-obturator or single-incision
  - Case-load
- 12% mesh related complications, 9% re-interventions
  - Altman RCT: 3% re-interventions
  - AMC Amsterdam: 2.6% re-interventions
High volume centers

The NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Anterior Colporrhaphy versus Transvaginal Mesh for Pelvic-Organ Prolapse

Daniel Altman, M.D., Ph.D., Tapio Väyrynen, M.D., Marie Ellström Engh, M.D., Ph.D., Susanne Axelsen, M.D., Ph.D., and Christian Falconer, M.D., Ph.D., for the Nordic Transvaginal Mesh Group*
Figure 1. Randomization and Follow-up of the Study Patients.
Subjective and objective cure in favor of mesh surgery

<table>
<thead>
<tr>
<th>Table 2. Primary and Secondary Outcome Measures after Colporrhaphy versus Mesh Repair for Anterior Vaginal-Wall Prolapse.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome Measure</strong></td>
</tr>
<tr>
<td>Successful composite primary outcome — no. of patients/total no. (%)</td>
</tr>
<tr>
<td>At 2 mo</td>
</tr>
<tr>
<td>At 1 yr</td>
</tr>
<tr>
<td>Prolapse stage 0 or 1 — no. of patients/total no. (%)</td>
</tr>
<tr>
<td>At 2 mo</td>
</tr>
<tr>
<td>At 1 yr</td>
</tr>
<tr>
<td>No symptom of vaginal bulge — no. of patients/total no. (%)</td>
</tr>
<tr>
<td>At 2 mo</td>
</tr>
<tr>
<td>At 1 yr</td>
</tr>
<tr>
<td>UDI summary score — mean (95% CI)</td>
</tr>
<tr>
<td>At 2 mo</td>
</tr>
<tr>
<td>At 1 yr</td>
</tr>
<tr>
<td>UDI-I subscale — mean (95% CI)</td>
</tr>
<tr>
<td>At 2 mo</td>
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<tr>
<td>At 2 mo</td>
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<tr>
<td>At 1 yr</td>
</tr>
<tr>
<td>PISQ-12 summary score — mean (95% CI)</td>
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<tr>
<td>At 1 yr</td>
</tr>
</tbody>
</table>
3% re-operation risk for mesh-related complications

<table>
<thead>
<tr>
<th>Variable</th>
<th>Colposcopy Group (N = 189)</th>
<th>Mesh-Repair Group (N = 200)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events related to surgical procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>between 2 mo and 1 yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>— no. of patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>1 (0.5)</td>
<td>3 (1.5)</td>
<td>0.62</td>
</tr>
<tr>
<td>Surgery for stress urinary incontinence</td>
<td>0</td>
<td>5 (2.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>Surgery for prolapse recurrence</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0.49</td>
</tr>
<tr>
<td>Revision of vaginal wound for mesh exposure</td>
<td>0</td>
<td>6 (3.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Pelvic or genital pain‡</td>
<td>0</td>
<td>1 (0.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Deaths‡</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
## Treatment benefit of mesh larger in primary surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Colporrhaphy Group (N = 189)</th>
<th>Mesh-Repair Group (N = 200)</th>
<th>Treatment Effect (95% CI)</th>
<th>Crude Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous anterior vaginal-wall repair</td>
<td>55/149 (36.9)</td>
<td>93/148 (62.8)</td>
<td>25.0 (14.3 to 37.6)</td>
<td>2.9 (1.8 to 4.7)</td>
<td>3.3 (2.0 to 5.6)</td>
</tr>
<tr>
<td>Recurrent anterior vaginal-wall prolapse</td>
<td>5/25 (20.0)</td>
<td>14/28 (50.0)</td>
<td>30 (1.9 to 58.1)</td>
<td>4.0 (1.2 to 14.8)</td>
<td>5.9 (1.6 to 26.8)</td>
</tr>
<tr>
<td>Previous pelvic-floor surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>37/115 (32.2)</td>
<td>69/106 (65.1)</td>
<td>32.9 (19.6 to 46.3)</td>
<td>3.9 (2.3 to 6.9)</td>
<td>4.5 (2.4 to 8.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>23/59 (39.0)</td>
<td>38/70 (54.3)</td>
<td>15.3 (−3.3 to 33.9)</td>
<td>1.9 (0.9 to 3.8)</td>
<td>2.9 (1.3 to 6.8)</td>
</tr>
</tbody>
</table>
Hypothesis 4

Registration of surgical outcome
Is the basis for change of infrastructure
Practice variation in POP surgery

Percentage operated per presentation

Number of POP procedures per 100 G25 for POP

- University hospital
- Teaching hospital
- Non-teaching hospital
Hypothesis 5

Mesh surgery is in its development phase
It will only get better
Outcomes improve over time
Continued improvement of mesh

- Huge potential in optimizing the biomaterial
- Continued improvement of restoring anatomy
- Animal models allow pre-clinical evaluation
- Coating technology of implants
- On demand resorption
Varying Fiber Densities for Multiple Surgical Meshes (Hernia and Prolapse Meshes)

Mass Density G/m²

- pelvitex
- gynemesh +m pre implant
- Gynemesh
- Prolene Soft
- gynemesh +m Post-implant
- Ultrapro
- IntePro Lite
- Novasilk
- Restorelle
- Coloplast
Foreign body response should be managed

Shortcomings current implant properties:

- Pronounced (chronic) inflammatory reaction
- Scar formation
- Biomaterial contraction
- Erosion

Lack of understanding of the influence of implant properties, foreign body reactions and daily loading on cell behaviour, tissue repair, and scar formation.
Technique of electrospinning

**Electrospun nanofibers**
Applying a voltage gradient between a target and a drop of polymer, either dissolved or melted

**Electrospinning setup**
The implant is composed by consecutive layers of randomly aligned nanofibers with porosities comparable to the diameters of the fibers and a large surface area.
Animal models
Surface technology

Biological peptides and substrates influence the molecular environment found in the ECM. They can eliminate biofouling by reducing cellular adhesion and subsequent fibrotic capsule formation. Hydrophilic surfaces exhibit decreased monocyte/macrophage adhesion.
On demand action
acoustic droplet vaporization

Ultrasound based mechanism
An emulsion is converted into gas bubbles upon exposure to ultrasound beyond a threshold pressure amplitude

Schematic representation of drug release by ADV in a hydrogel scaffold. Bottom: A water-in-PFC-in-water ($W_1$/$PFC/W_2$) double emulsion, containing a growth factor in the $W_1$ phase, is encapsulated within the scaffold. Upon exposure to acoustic amplitudes greater than the ADV threshold of the emulsion, the PFC within the droplets is vaporized, thus releasing the $W_1$ phase. Top left: confocal fluorescence image (fluorescein, shown in green) of a PFC double emulsion droplet (scale bar = 10 μm). Smaller aqueous droplets, containing a water-soluble payload such as fluorescein or bFGF, are enveloped by a larger PFC globule. Top right: visible image of a 10 mg ml$^{-1}$ fibrin gel containing 5% (v/v) double emulsion after targeted exposure to ultrasound. The “block M” consists of gas bubbles generated by ADV. Scale bar = 4 mm.
In vivo tissue engineering

Patient with muscle defect → Biocompatible 3D-Matrix → Muscle biopsy

Bioreactor in vitro → Cell differentiation

Muscle tissue construct → Muscle tissue generated in vivo

Patient as "Bioreactor" → Cell differentiation

Muscle biopsy → Cell-matrix application

Myoblast cell culture → Muscle tissue generated in vivo
Take home message

- We should stop dichotomizing the mesh debate
- Mesh is in it’s development phase
- In the end it will be good enough for primary surgery
- On the short term: focus on infrastructure
- On the long term: focus on improving the biomaterial