SCENIHR Preliminary Opinion on

The safety of surgical meshes used in UroGynecological surgery

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Comments from Pr Bernard Jacquetin,

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Foreword:

I will limit my comments to the POP surgery; the SUI surgery is not, today, very controversial and, as a gynaecologist, I am not interested by males!

Disclosure:

I am the Prolift™ patent’s owner, but this device was withdrawn from the global market in March 2013; so I have no more conflict of interest to declare...

General assessment:

My global feeling is “half-hearted”:

- Reassured by this European opinion less negative than the US one, particularly the FDA warnings, and by the reasonable general recommendations.
- Disappointed by the lack of a clear conclusion:
  - Even the UK’s MHRA recently concluded that the vaginal mesh usage benefits outweigh the risks
  - The SCENIHR, repeating many times that the benefits/risks balance should be acceptable, didn’t give a clear evaluation, and even a conflicting opinion particularly evident concerning the vaginal mesh indications:
    - In the abstract (P.5, L. 4-5): “...the use of synthetic mesh for POP repair via a transvaginal route should only be used when other surgical procedure have already failed or are expected to fail.”
    - In the executive summary (P.8, L.16-17): “In the context of POP, the use of mesh placed by the vaginal route is only recommended as a secondary choice after failed primary surgery.”
    - It’s a MAJOR difference about indication!
The literature review, excepted for the experimental research, is largely dominated by the comparative studies; in my opinion, the EBM is not limited to the RCTs but have to take in consideration a huge number of observational studies giving the “true life” of the surgical devices usage, particularly for the long time follow-up.

The opinion text is not homogeneous, probably due to the juxtaposition of the different contributions, reason why there are a lot of repetitions, sometimes only annoying (like the role of the mesh size...), but sometimes disturbing (for example the patient risk factors are different in number but also in quality according to the different chapters). A synthesis work appears desirable...

Detailed assessment:

- **ABSTRACT:**
  - P.4: “colposuspension is associated with greater surgical morbidity” is not at a good place in the transvaginal surgery chapter.
  - P.5: do you confirm “or are expected to fail” (See above)

- **1. EXECUTIVE SUMMARY:**
  - P.7, L.41: the Directive 93/42/EEC (including amendment 2007/47/EC) (also mentioned P. 17 etc.. ) in not provided in Annex
  - P.8, L. 17: add “or are expected to fail” (see above)
  - P.8, L. 33: there are absorbable (partially or totally) synthetic meshes
  - P.11, L.16: “Taking into account the lack of long term data...” and P.11, L.29-30: “establish scientific studies to assess the long term (at least 5 years) safety and performance...”;

- **2. BACKGROUND:** no comment

- **3. TERMS OF REFERENCE:** no comment.

- **4. SCIENTIFIC RATIONALE:**
  - P.17, L.25: concerning the national standard in France (AFNOR S94-801), it’s inaccurate to mention “for stress urinary incontinence”; this norm is dedicated to SUI and/or POP (see slide 1, inner part).
  - P.29, L.22: please add pore...“mesh PORE size”
  - P.31, L.1-3: the Figure 1 is not understandable: 7 different meshes are mentioned but only 4 curves are on the graph?
  - P.33, L.15-34: it’s a good synthesis of the host response to implanted biomaterials.
P34, L.15: the sentence is incomplete
P.34, L.24: correct “bowel INJURY”
P.34, L.41: be careful with the abbreviation SIS, used in the text with two different meanings: “Single Incision Slings” and “Small Intestine Submucosa”.
P.51, L.18: I cannot understand why and how, in a multiple compartment repair (according to Table 3) including anterior AND posterior mesh, there are *de novo* POP in untreated compartments?
P.51, L.23-24: I agree totally with the lack of long term results of RCT; it’s a very important weak point well illustrated in this paper from OU et al (Ou R, Xie XJ, Zimmern PE: *Prolapse follow-up at 5 years or more: myth or reality? Urology* 2011, 78:295-299.)
P.52, L.36-40 and P.53, L.1-19: I don’t understand at all, in the UK guidelines, the reason and the interest of this long chapter about infracoccygeal sacropexy, compared to other guidelines (US, Dutch, French…) only quoted; I will come back later (P. 59) on the UK’s recommendations.
P.55, L.8: could you clarify the meaning of “decade”: 10 days, 10 years or 10 operations?
P.55, L.30: clarify this Error!
P.58-60: Risk assessment and recommendations by National Associations: Important comments about French recommendations (erroneous!) and UK recommendations (NOT mentioned!)
- P.58, L.35-40 and P.59, L.1-3: I disagree totally with the abstract of the French National Authority for Health (HAS), particularly the point 3) “the use of polypropylene meshes for POP surgery by vaginal route was not recommended”. In 2006 the HAS conclusion was “vaginal meshes are in the field of the clinical research”, but in January 2008, the conclusion was “vaginal meshes may have an interest in case of recurrence or in a particular clinical situation increasing the recurrence risk” (see slide 1, upper part), i.e. *exactly the same conclusion* than the today SCENIHR’s one (if you maintain “...are expected to fail”).
- P.58-60: There are recommendations from France, USA, Australia/New-Zealand, Canada, Australia again, but NOTHING from UK! It’s a pity, because this country, although considered doing less vaginal mesh implants than all others OECD countries (about 3.3% for anterior repair) according to Haya et al (Haya N, Baessler K, Christmann-Schmid C, Tayrac R, Dietz V, Guldberg R, Mascarenhas T, Nussler E, Ballard E, Ankardal M, Boudemaghe T, Wu JM, Maher CF: *Prolapse and continence surgery in countries of the Organization for Economic Co-operation and Development in 2012. Am.J Obstet.Gynecol* 2015), published very good reviews and recommendations, particularly:
  - The NICE in 2008 published a very complete review with clear comparisons between the different implants compared to autologous repairs (see slide 2 for a short abstract)
  - The MHRA produced this year a large compilation with a “courageous” conclusion: “…on the safety of vaginal mesh implants and their use and has concluded that, from a regulatory perspective, **the benefits of the use of these devices outweigh the risks.**” (see slide 3)
5. OPINION:
   o 5.1. Terms of reference:
     ▪ P.61-64: The answers to the questions Q1-Q8 are very similar, but not exactly identical to those in the P.8-11; a little bit disturbing...
   o 5.2. Recommendations:
     ▪ I agree with these general recommendations, quite similar to these mentioned P.11 excepted improved technologies...Why?

My personal (expert?) opinion:

I am sorry to have to defend a personal work, but I can hardly understand why one of the rare available studies with 5 years follow-up was never so much as cited...difficult to admit it’s not unbiased!

All the health regulatory agencies and all the national and international scientific societies are asking for premarketing evaluation of the new devices and for long term data (very often mentioned in your opinion)...

After asking in 2000 to Ethicon not to put on the market our TVM prototype before 5 years (the Prolift™ was supplied in March 2005), we (the French TVM group) began in 2004 a prospective study, in parallel with an US group headed by Dennis Miller (85 and 90 patients in each group):

- Prospective non comparative studies
- Without conflict of interest:
  o The support from Ethicon was limited to
    ▪ Sponsoring of the meetings between the 9 members of the TVM group
    ▪ Statistical counselling
    ▪ English translation
  o The Prolift™ patent was delivered only in November 2006.
- In the “worst” conditions:
  o Hand shaped heavyweight mesh
  o Systematic concomitant hysterectomy (the only difference with US patients was the largely different rate of previous hysterectomies!)
  o Beginning of the surgeons experience cause of the lack of knowledge about the preventive techniques of mesh exposure, progressively discovered
  o Reason why the mesh exposure rate was as high as respectively 15,6 and 18,8%, but also proving the...honesty of the results!
Published by the two teams at 1, 3 and 5 years of follow-up:


- Showing very similar results and particularly a very stable anatomical result (nearly 90% success rate) with time which was, of course, the major aim of a reinforcement mesh...isn’t it?
  - The slide 4 is a comparative table of the two studies results
  - The slide 5 is an abstract of the main results and complications of the two studies
  - The slide 6 is a synthesis of the sexual consequences of the TVM in the two countries.

- We are today planning to control these patients with 10 years of follow-up...

With our huge experience, we are convinced that the anterior TVM is able to compete with sacrocolpopexy, particularly in case of large cystocele (and even more in case of paravaginal defect); I tried to represent on the slide 7 the cumulative cure rate of these two operations.


To finish, if you are really interested by my expert opinion, you can find joined what I wrote, one year ago, for the EUGA newsletter...the first section was dedicated to the SCENIHR’s work!

After a chapter concerning the complications, I tried to update the indications and contraindications, with references to HAS recommendations and AFNOR standard norm for France and to the IUGA roundtable as in your Opinion. I added my own (expert?) opinion about these recommendations.

My conclusion was:

- It appears difficult to us not to admit that the vaginal surgery remains the most “minimally invasive” approach
- We have hard time to believe that the concept of the TVM can be challenged on an anatomical standpoint as it replicates the normal anatomy as confirmed by cadaveric dissections. The lateral vaginal defect is not corrected by the abdominal access unless if combining a concomitant technique of paravaginal repair.
- And we plead for the need to assess the results of the TVM operations in the long term because they were designed to reduce recurrences which in their vast majority only appear 3 to 5 years after traditional interventions in the absence of technical defects.

It’s the reason why I tried to convince you of the importance of our 5 years follow-up work!
Slide 1: in France, recommendations from the Health authority (HAS) and from the AFNOR norm concerning vaginal implants for SUI and/or POP.
Slide 3: in UK (2): the very recent MHRA recommendations about vaginal mesh implants (2015)
## Long term results (1)

### TVM US and France 5 years results
(January-December 2004)

**US study:** 3 centers, 85 patients, 5 reop for POP, 9 partial mesh excision, 3 reop for complications, exposure rate 18.8%

**French study:** 8 centers, 90 patients, 4 reop for POP, 7 partial mesh excision, 1 reop for complication, exposure rate 15.6%

<table>
<thead>
<tr>
<th>Leading edge (cm)</th>
<th>Baseline n=90</th>
<th>1 year n=87</th>
<th>3 years n=83</th>
<th>5 years n=71</th>
<th>7 years n=82</th>
<th>9 years n=64</th>
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<tbody>
<tr>
<td>-3</td>
<td>0</td>
<td>42 (48)</td>
<td>40 (47)</td>
<td>38 (46)</td>
<td>32 (48.5)</td>
<td>32 (42.6)</td>
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<tr>
<td>-2.5 to -1.5</td>
<td>0</td>
<td>29 (33)</td>
<td>28 (33)</td>
<td>27 (33)</td>
<td>19 (28.8)</td>
<td>19 (28.8)</td>
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<tr>
<td>-1 to 0</td>
<td>3 (3)</td>
<td>9 (10)</td>
<td>7 (8)</td>
<td>6 (7)</td>
<td>8 (12.1)</td>
<td>8 (12.1)</td>
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<tr>
<td>0</td>
<td>7 (8)</td>
<td>5 (6)</td>
<td>7 (8)</td>
<td>6 (7)</td>
<td>6 (7)</td>
<td>6 (7)</td>
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<tr>
<td>+0.5 to +1</td>
<td>5 (6)</td>
<td>11 (12.9)</td>
<td>11 (12.9)</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>+2.5 to +3</td>
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<td>12 (14.1)</td>
<td>12 (14.1)</td>
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<td>10 (56)</td>
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</table>

| Re-intervention  | —            | —          | 1 (1)       | 1 (1)       | 1 (1)       | 1 (1)       |
| Success rate     | —            | —          | 92% (95%)   | 96% (95%)   | 97% (95%)   | 97% (95%)   |
| Leading edge <0  | —            | —          | 85-96% a    | 89-99.2% a  | 81-94% a    | 82-96.8% a  |
| (90% CI), %      | —            | —          | 88% (95%)   | 91% (95%)   | 87% (95%)   | 89-96% a    |
| Bulge symptoms   | 85/89 (96)   | 2/81 (2)   | 1/83 (1)    | 4/79 (5)    |
| Composite measure of success b | 0 | 73/81 (90) | 73/83 (88) | 67/80 (84) | 75-90% a |
|                  |              | 83-95% a   | 80-93% a    | 75-90% a    | 75-90% a    |

### Anatomical and functional results in relation to the leading edge at 1, 3 and 5 years

<table>
<thead>
<tr>
<th>Anatomical and functional results</th>
<th>US study</th>
<th>French study</th>
</tr>
</thead>
<tbody>
<tr>
<td>a exact asymptotic binomial 90% confidence limits</td>
<td>85-96% a</td>
<td>89-99.2% a</td>
</tr>
<tr>
<td>b composite measure of success defined as: leading edge above hymen (&lt;0) with no bulge symptoms and no reintervention for prolapse</td>
<td>88% (95%)</td>
<td>91% (95%)</td>
</tr>
</tbody>
</table>

**Miller D., Lucente V., Babkin E., Beach P., Jones P., Robinson D.:** Prospective clinical assessment of the transvaginal mesh technique for treatment of pelvic organ prolapse: 5-year results. *Female Pelvic Med Reconstr Surg* 2011, 17:139-143.


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**Slide 4:** Long term results (1); comparative table of the anatomical, functional and composite results for the US and French studies at 5 years follow-up.
Slide 5: Long term results (2); abstract of the US and French studies main results at 5 years follow-up.

French study:
- 8 centers, 90 patients
- 4 reop for POP, 7 partial mesh excision, 1 reop for complication
- Exposure rate 15.6%
- Anatomical success: 87.0%
- Lost of follow-up: 8/90 (8.9%)  

US study:
- 3 centers, 85 patients
- 5 reop for POP, 9 partial mesh excision, 3 reop for complications
- Exposure rate 18.8%
- Anatomical success: 89.4%
- Lost of follow-up: 19/85 (22.4%)  

Slide 6: Long term results (3); comparison of the sexual results of the US and French TVM studies at 5 years follow-up.


Slide 7: Long term results (4); Comparative evolution of time to prolapse recurrence of an anterior vaginal mesh (overall prolapse on the left, compartmental prolapse on the right) and of a sacrocolpopexy.
Current indications and contraindications on mesh use in prolapse repair.

When you will read these lines, the European Commission SCENHIR (Scientific Committee on Emerging and Newly Identified Health Risks) will have begun its evaluation of the safety of surgical meshes used in urogynecologic surgery which is due by January 2015. Obviously, being the inventor of the Prolift™ device, I do not belong to this commission because of a potential conflict of interest. This device was withdrawn from the market in March 2013 and I do not have any more direct financial interest to argue in favor of its use! Hopefully, the opinion of the SCENIHR will be more balanced than the FDA's in the United States and will not generate the same “wind of madness”: outburst of the media, solicitation of patients for joining class actions, multiplication of lawyers convinced that there is much money to gain! Irony of fate, the first Prolift™ provisional patent application filed in 2002 and accepted in November 2006 in the USA, was granted in Europe on December 30th, 2011...

The TVM complications:

There is no doubt that the use of prostheses can lead to specific complications and this has been well documented by several studies. The most common is the vaginal exposure which has wrongly been put ahead while the more frightening peri-prosthetic contraction have been ignored for a long time, even by FDA! Within our French group, we have recognized these complications at a very early stage thanks not only to our anteriority in the use of vaginal meshes but also because of a “specialised centers effect” which gave us in Lille and Clermont-Ferrand the opportunity to treat a large number of them. This is why Michel Cosson and myself, we felt authorised to say and write in an international journal in 2009 that these complications “were at the same time over-estimated in frequency, often poorly described, sometimes overemphasized and incorrectly managed”. We definitely had to work at improving the safety of the patients. A very detailed classification of these complications came out after a collaborative work of the IUGA and ICS. Many comparative studies recalled us not to forget that the traditional techniques also had significant rate of complications. In addition, several national registries have objectively assessed the rate of these complications, the latest being the Austrian register gathering
726 vaginal mesh interventions with 6.8% of per and postoperative complications, a rate of 12% of vaginal exposures and 10% of dyspareunia.

Does this justify to give up using vaginal meshes, as some people would suggest? In my opinion, this would be a major step-back which only interest would be to rejuvenate me by resurfacing the techniques we used 2 or 3 decades ago! It is clear that the science of mesh is still in its infancy and I am quite convinced that, in a few years, stem cells will replace the derivatives from oil products...

**Current indications and contraindications:**

This is the question I have been asked to answer but perhaps, in the current hostile context, would it be better to speak about recommendations rather than indications...

In my country, since 2008, the French health authority (HAS) did not take a clear position. It first stated in 2006 that the use of meshes has to be considered as clinical research. In a further and rather vague statement, it stated that the use of vaginal prosthesis could have an “interest for recurrent cases or if there were good clinical reasons to suspect that the patient presented a high risk of recurrence”. In order to refine its opinion, this organization had required a review of the literature which was carried out by our group.

In the lack of further action from the HAS, together with a colleague urologist, Pr François Haab, we took the responsibility to gather a working group (surgical experts and deeply involved manufacturers) in order to establish a standard (AFNOR norm NF S94-801) detailing both preclinical and clinical studies to be carried out before introducing any new products on the market, as well as the post marketing surveillance. One can note that our 2007 proposals were very close to the FDA’s requests in 2011! Unfortunately, the application of these French standards were not mandatory and thus they failed to slow down the uncontrolled introduction of a multitude of devices on the French market (60 were indexed!) based on the concept of “equivalence” which hopefully will disappear at some stage in the near future.

In this context, we drafted a proposal of consensus and submitted it for validation to four French scientific societies by December 2008. In this document, we had suggested the following indications:

- **Beyond the hymen-cystocele**, especially its lateral type (paravaginal defect): anterior TVM
- **Severe prolapse associating several compartments** including an exteriorised cystocele: anterior and posterior TVM or total TVM
- And especially **recurrent prolapse** (in particular if the previous operation had been correctly carried out): anterior OR posterior TVM

We emphasized the need to take into account the risk factors weighing on this indication: family history, high ligamentous laxity, severe muscular avulsion of the levator ani muscles, high abdominal pressure, collagen abnormalities...
This multi-factorial approach of the indication was further discussed during a round table organised by the IUGA in 2010 under the direction of Willy Davila. A report was published in 2012. It states that it is necessary to take into account various risk factors (age, recurrence on the same compartment, importance of the cystocele, mobility of the apex, defect of the posterior compartment, defective fascia, abdominal high pressure, local or systemic painful syndrome, desire of pregnancy as well as the combination of a recurrent or bulky cystocele with one or more of these risk factors) before proposing the use of a mesh which could be depending on the individual situation likely beneficial, possibly beneficial, unlikely beneficial or not recommended.

The contraindications which we proposed were supported by the panel: young age, desire of pregnancy, severe immunodepression, long term corticoid therapy, non-controlled diabetes, heavy smoking, and previous pelvic irradiation. We did not include obesity (BMI > 30) despite a well-known increased risk of mesh exposure risk as weight excess is also a poor indication for an abdominal approach. Vulvar, vaginal or LUT infections, severe vaginal atrophy and/or vaginal ulcerations were considered as temporary contraindications.

We have had to wait until 2013 in order to get a consensus from the National College of the French Gynecologists and Obstetricians (CNGOF) “Indications of mesh in surgical treatment of pelvic organ prolapse by vaginal route” after it made comments about the “Prevention of complications related to the use of prosthetic meshes in prolapse surgery: guidelines for clinical practice” based on the national literature in 2011 and the European one in 2012. This consensus led to 10 proposals.

My Expert Opinion:

I all the more subscribe to these recommendations for which I was a proof-reader. To add my expert opinion there, let me say once again that:

- The chronic painful patient (chronic pelvic pain, fibromyalgia, dyspareunia…) must be excluded from vaginal prosthetic repair. Let us go even further: patients whose mind does not appear solid enough to face the potential complications must be excluded. This reinforces the concept that the decision must be tailored to the patient after a long discussion.
- The ideal indication is a bulky anterior recurrence, after a correctly carried out first intervention. This is the proof of the existence of a tissue deficiency. A patient who is facing a 2nd or 3rd recurrence generally accepts the risks of a prosthetic operation in the hope of putting an end to her concern. This was recently emphasized by a study comparing 668 patients without previous prolapse surgery to 142 patients with a recurrence which showed that the rates of vaginal exposure were respectively of 10,6% and 2,8%, leading to the conclusion by the authors that the presence of scar tissue is probably protective against the mesh exposure.
- When a true connective tissue abnormality of genetic cause is present, the indication of a prosthetic reinforcement is a clear need, but most of the surgeons will prefer a
laparoscopic approach in order to prevent any risk of dyspareunia as most of the time, these patients are young patients with an early recurrence and an history of familial prolapse.

- The anterior paravaginal defect remains, in our opinion, an ideal indication. Nevertheless, the diagnosis either by clinical examination or by imaging is difficult. It is often during the course of the operation that one discovers that the vesical fascia is partially or completely detached from its lateral insertions. Pelvic floor echography which makes it possible to precisely identify the “indirect” signs (importance of the muscular avulsions, dimensions of the levator ani muscles hiatus, lack of fixity of the vaginal culs-de-sac) is the key preoperative examination. Some publications clearly demonstrated the interest of a prosthetic reinforcement in these situations.

- Uterine preservation must be considered, in agreement with the patient, each time the uterus and the ovaries are free from pathology

- The use of a posterior mesh should not be prohibited although the literature specific to the posterior compartment is scarce. Our experience shows that there are rather less complications with the posterior meshes than with the anterior, perhaps just because their surface is less important. It is in fact the trans-gluteal and trans-sacrospinous access that many surgeons fear... Nevertheless, when the anterior prosthesis is effective, the posterior compartment is threatened: 1/3 of our “failures” are in fact a decompensation of the compartment which has not been repaired. This is documented in some publications.

- The management of the prosthetic complications, in particular of the severe retractions, must be made by an experienced team to limit the number of reoperations. It is a matter of fact that often the problem cannot be solved in a single procedure, but undoubtedly it should not either require ten or more reoperations! A recent study showed that 60% of 347 patients presenting prosthetic complications had required two or more operations.

- To conclude:
  - It appears difficult to us not to admit that the vaginal surgery remains the most “minimally invasive” approach
  - We have hard time to believe that the concept of the TVM can be challenged on an anatomical standpoint as it replicates the normal anatomy as confirmed by cadaveric dissections. The lateral vaginal defect is not corrected by the abdominal access unless if combining a concomitant technique of paravaginal repair.
  - And we plead for the need to assess the results of the TVM operations in the long term because they were designed to reduce recurrences which in their vast majority only appear 3 to 5 years after traditional interventions in the absence of technical defects.