EXPERT REPORT BY THE

International Urogynaecology Association (IUGA) in response to the

Scientific Committee on Emerging and Newly Identified Health Risks

SCENIHR

Preliminary opinion on: -

The safety of surgical meshes used in urogynaecological surgery

This report has been prepared by

Dr Mark Slack,

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And

Dr G Willy Davilla

On the instruction of

The President and Executive Board of

The International Urogynaecology Association

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The International Urogynaecology Association

The International Urogynecological Association (IUGA) is the largest global professional association of Female Pelvic Floor Medicine clinicians and researchers, with a membership of over 3000 from all corners of the world. It is host of the premiere annual scientific meeting in this field and publisher of the principal scientific journal in the field (the International Urogynecology Journal).

This commentary is brought forth on behalf of IUGA's membership and has been approved by its Board.

DECLERATION OF AFFILIATIONS AND CONFLICT OF INTERESTS OF REVIEWERS

Dr Mark Slack

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Title: Dr

Profession Consultant Urogynaecologist

Declaration

MCS has previously been speaker and/or consultant for Johnson and Johnson, Boston Scientific Corporation, Pfizer, Astellas and Lilly Pharmaceuticals. He currently holds no grants of financial agreements with any commercial companies. He has given expert advice in the Supreme court in the United States of America in mass tort litigation cases.

Prof Jan Deprest

Position	Professor of faculty of Medicine Head centre for surgical technologies Chair of Dept of Development and Regeneration Catholic University of Leuven, Belgium
Title	Professor
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Declaration

The research program of Prof Deprest has been supported by unconditional grants from Bard (Olen, Belgium), Johnson & Johnson Medical (Norderstedt, Germany), FEG Textil technik (Aachen, Germany), and Blasingame, Burch, Garrard, and Ashley (Atlanta, GA). Those agreements were handled via the Leuven Research and Development transfer office. Those sponsors did not interfere with the planning, execution, or reporting of the research neither own the results. JD has been speaker and/or consultant for Bard, Johnson & Johnson Medical, American Medical Systems, and Blasingame, Burch, Garrard, and Ashley.

Dr G Willy Davilla

Position	Chairman of the Department of Gynecology and Head of Urogynecology and Reconstructive Pelvic Surgery at Cleveland Clinic Florida in Weston/Fort Lauderdale, Florida. Associate Director the Fellowship training program in Urogynecology and Reconstructive Pelvic Surgery
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Declaration

Dr Davilla has been speaker and/or consultant for AMS, Pfizer, Astellas, Allergan, CL Medical and Uroplasty. He has received research grants from Coloplast, AMS, Pfizer and ACell. He has been a party to Intellectual Property licensed by the Cleveland Clinic Foundation to AMS. He is the Past-President of IUGA.

INTRODUCTION:

Although much of the recent medicolegal activity has focused on the use of meshes in urogynaecologic surgery it is curious that the paper restricts its reflections to urogynaecological and urological surgery. As such the title is misleading and should be “The safety of meshes used in surgery”, or “The safety of surgical meshes used in urogynaecological surgery, urological surgery and general surgery”.

The paper does cover urological surgery but for completeness should include a section on mesh use in hernia surgery especially inguinal hernia surgery, if only for reference purposes. The complications experienced in hernia surgery reflect those seen with vaginal surgery often with greater problems with pain. This literature makes an important comparator both because of the frequency of the surgery and the significant complication rate.

We believe that the time allowed for external review and return of comments is too short. We advise an extension so that the respective learned bodies have time to make an appropriate response.

It is our understanding that the PROSPECT study is likely to be published in 2015. This will contain data essential to the clinical discussion and we wondered whether the SCENIHR should delay the publication of the final report till this data is available.

SCIENTIFIC MERIT:

There is no description of the methodologies used to conduct the literature search or how the data was graded. It is difficult to know what process was used to determine which data was included or more importantly what method was used to exclude papers. At best it is therefore a document providing

“expert opinion” except that apart from three of the external experts this report has been drawn up by people with little expertise in the basic science or clinical areas discussed.

A more open reference to how the conclusions of this document reflected the available published systematic reviews, documents in the Cochrane library and NICE guidelines would have been useful.

EXTERNAL EXPERTS:

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It is important that the report describe the selection process used to pick the external experts and more importantly to highlight the factors that were used to exclude experts.

The reviewers expressed surprise at the makeup of the external experts. They seem to have been selected ahead of many more prominent experts in the field of alloplastic and mesh materials. It is also surprising to see that two members of the external experts are from the Therapeutic Goods Administration (TGA) in Australia. As such it is of concern that their opinion may reflect that of a regulator rather than a scientist. It also seems to give excessive influence to a single organization.

It is also important to know if industry had any part in the nomination or selection of members of the expert group.

We are not sure that the declaration is entirely accurate for all the members. Perhaps members could review their declarations and ensure there are no omissions.

Prof Sheila MacNeil has not declared her affiliation.

RECOMMENDATIONS FOR SUBJECT MATTER TO BE INCLUDED IN THE REPORT:

We are surprised that the committee has made no comment on the method of introduction of mesh materials and new surgical procedures. In its current format it looks as if the committee is giving its support to the current regulatory requirements of the FDA and the CE marking process. This area needs to be addressed if we are to avoid the sort of problems experienced with the mesh materials and kits.

We would strongly recommend that the SCENIHR working group and experts include a section in this paper with recommendations for the safe and ethical introduction of these products. We recommend that they use the guidelines of the IUGA round table conference as a template(1). It is important that the committee emphasizes the importance of each manufacturer being responsible for the animal studies with their own products as well as the appropriate human clinical trials which should be reported ahead of random introduction and marketing.

Failure to address this issue will make the paper little more than a summary of the current literature and act as a barrier for the safe and ethical introduction of newer products and operations.

The section on consenting should be expanded and could again benefit from including the recommendations from the 2nd IUGA Grafts Round Table meeting(2)

The section on patient selection and patient factors could also benefit from the inclusion of the recommendations from the 2nd IUGA Grafts Round Table meeting(3)

It is also our opinion that any progress needs to be made here in collaboration with the industry. A framework for creative, positive, realistic, yet transparent, and controlled collaboration needs to be set up. It combines expertise from both sides. It would seem that the SCENIHR kept out“experts” who had any links with the industry with subsequent loss of expertise.

STATEMENT ON TYPES OF MATERIAL

Based on a literature search on the term “polypropylene” (page 26), the report concludes that, based on the assessment of risks that polypropylene (PP) type 1 implants are the most appropriate synthetic meshes for vaginal use and PP type 1 and polyester type 3 for insertion via the abdominal route. To our knowledge, there is no credible evidence at this stage that the polymer choice itself determines the

complications risk, as suggested by the report (page 31). In reality PP is the most widely used for any type of implant in reconstructive surgery and the reason for that is merely historical and economical. PP is certainly not exempted from complications, and one could even argue inversely: PP is actually the polymer that numerically is most frequently associated with clinical problems (4, 5). At this moment the use of PP per se is questioned in the ongoing class actions in the U.S.A., because documents have been found that the manufacturers of the raw material used for production of the PP fibers, never meant PP to be used clinically (see below). Also, the long term stability of PP-filaments has been questioned because of submicroscopic degradation (4), again, best documented for PP. It is our opinion that it is unclear whether this translates to the later occurrence of clinical problems.

It is important to remember that Chevron Phillips the manufacturers have made a statement that none of their polymers should be considered safe for temporary or permanent implantation in the body. They assert that the proof of safety of products implanted in the human body remains the responsibility of the manufacturers implanting the products. In essence this means that any company selling a polypropylene implant has to provide its own clinical data on safety. This has already been tested in court in the United States of America. In many ways this overrides the FDA 510K certification where companies rely on data from other products to claim equivalence. While it is to be remembered that this is a standard disclaimer used by the company in respect of all of their polymers and co-polymers it is impossible for companies to ignore this statement and therefore should provide both human and animal data to support the safety of their respective products. (http://www.jurilytics.com/downloads/wise-v-cr-bard-post/brennan-report.pdf)

Along the same lines, the (abdominal) insertion of polyester implants receives credit in the report, for which no reason or literature is given. This product is used frequently in some geographical areas of Europe, but to our knowledge there are no references known to us that justifies this polymer to be better than any of the others used elsewhere.

Conversely it seems that the textile characteristics of the implant in the widest sense of the word, are more likely to play a very important role in the biomechanical behavior (6, 7). There is ample translational research evidence that demonstrates that the textile properties influence the host response. It is hence logic to assume that it determines eventual clinical outcome, as history has learnt (1). Initially most attention was given to use monofilament rather than multifilament products, and to use rather large pore size products, later to reduce the density of the material, where at this moment we are understanding that also the pore stability plays as important a role in the integration into the body (1, 6). Clinically, several polymers alternative to PP have been used. There have been several including polyester. Some of these have in vitro better biomechanical characteristics and in vivo induce a lesser inflammatory response.

We have tested some of these materials, though the examples below are not exhaustive. For example, polyvinylidene fluoride (PVDF) experimentally induces a lesser inflammatory response, has a higher elasticity and tensile strength thus achieving appropriate textile properties with thinner fibres and less material. The latter is in line with the recommendations to limit the load of foreign body in the patient (8). Another method used to reduce the load of material to the host, is to add filaments of a second, yet resorbable polymer. The best studied to our knowledge, is the addition of poliglecaprone to PP, a polymer very widely used as resorbable suturing material. The added filaments stabilize the initial construct, makes surgical handling of a very light implant possible, reduces the inflammatory response and determines eventual biomechanical outcome (9). Though this makes that implant “hybrid”, that

type of hybrid is completely different than for instance adding an acellular collagen matrix to a synthetic durable mesh – which experimentally adversely affects outcome (10).

This report treats all products that combine different constructs as the same, which is an oversimplification. Actually, progress is expected from adding bioactive properties to the filaments (7).

In conclusion we reject the recommendation that Polypropylene is safe for vaginal use or that polypropylene and polyester are suitable for abdominal use without consideration of any other materials as this is not based on any translational or clinical evidence, and therefore cannot be defended. The statement endorsing just two materials risks arresting the quest for better polymers as well as textile constructs – a need everybody agrees is vital.

Obviously any alternative claims for new materials should be properly evaluated– for instance using the pipeline earlier described by the IUGA mesh round table.

In some countries, as Belgium, the statement endorsing Amid type I PP implants and polyester has outlawed the use of non PP products. This is a retrograde step and one which will hamper scientific advancement in the field. This does not reflect the current understanding of the technology and science behind this subject.