The Independent
MEDICINES & MEDICAL DEVICES
Safety Review

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Written Evidence

Properties of mesh

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Declaration of Interests

Dr Jan Willem Cohen Tervaert
I have no conflict of interest.

Dr Chris DeArmitt
I was expert witness in a class action litigation in the USA on behalf of plaintiffs and we won settlements for about 9000 women. At present I have no paid activity in mesh. I am providing my expert opinion free of charge and without conflicts of interest.

Dr Vladimir Iakovlev
My potential conflict of interest is that I provided assessments for medicolegal cases for pelvic mesh litigation. The requests for all cases were from plaintiffs' attorneys and I've been compensated for my work at hourly rate independent from the outcome of litigation.

Prof Vikram Khullar
NIL

Dr Mark Slack
Until July 2019 I was employed by Cambridge University Hospitals NHS Trust. In addition I am a shareholder and employee of CMR Surgical. I have not received any Pharmaceutical consultancy fees since 2012. Prior to that I received limited consultancy fees for the work undertaken in a clinical trial. I have never received any royalties from a Pharmaceutical company. Any publications have been my own. I have published extensively on mesh including:- • Histological description of tissue reaction to mesh - **Slack M,** Sandhu, JS, Staskin DR, Grant RC In vivo comparison of suburethral sling materials. Int Urogynecol J. 2006; 17: 106-110

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- Tincello D, Kenyou S, **Slack M**, Toozs-Hobson, Mayne C, Jones D, Taylor D Colposuspension ot TVT with anterior repair for urinary incontinence and prolapse: results and lessons from a pilot randomised patient-preference study (CARPET 1) BJOG 2009DOI:10.1111/j.1471-

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- An evidence based publication on the management of mesh complications. Cundiff, GW, Quinlan DJ, van Rensburg, JA, **Slack, M** Foundation for an Evidence Informed Algorithm for Treating Pelvic Floor Mesh Complications: A Review BJOG. 2018 Jan 31. doi: 10.1111/1471-0528.15148.

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- **Slack M** Vaginal Mesh Surgery In Medicolegal Issues in Obstetrics and Gynaecology Jha S, Ferriman E Springer (Eds) 2018 ISBN 978-3-319-78683-4
- Bolton H, **Slack M** Mesh Tape Exposure Following Tension-free vaginal Tape. In: Coomarasamy, Shafi, Davila and Chan (Eds) Gynaecological and Obstetric Surgery – Challenges and management options. Wiley Blackwell, Oxford UK. 2016 356-360
- **Slack M**. Synthetic materials for pelvic reconstructive surgery. In: Cardozo L and Staskin D. (Eds) *Textbook of Female Urology and Urogynaecology.* Abingdon. Informa Healthcare. 2006 835-844
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Properties of mesh – transcript

START OF TRANSCRIPT

Cyril Chantler: It's just 5:00 o'clock.

Julia Cumberlege: Yes, we are slightly ahead of time, it's just 5:00 o'clock now in London. Perhaps we could anyhow make a start. I'm Julia Cumberlege, and I've been asked to chair the review into three different areas: Primodos, sodium valproate, which are both medications, but the one that we're really interested in today is about surgical mesh, and that's what we're going to be exploring.

I ought to just tell you that this conversation we're going to have today will be transcribed and put online. This is a recording, but we're not screening it in terms of a video, or anything like that. It's simply an audio recording. I hope that's all right with all of you who are here.

The second thing is that we would like a declaration of interest later on sent to us, because it's important when we meet patient groups et cetera, that they can see what the interests are of those that are taking part.

I have to say that we've had a lot of opinions, a lot of experiences which have been put to us by, particularly, patient groups, which we would like your views on. We'd particularly like to discuss with you if the properties of mesh make it inherently unsuitable or suitable for insertion for stress urinary incontinence. My first question to you - and I'll go and ask each of you for your views, whether you think the properties in mesh make it inherently unsuitable or suitable for insertion for SUIs.

Perhaps I could start with Doctor Chris DeArmitt from the USA.

Chris DeArmitt: Hello.

Julia Cumberlege: Hello.

Chris DeArmitt: Thank you. Yes, I'll give one minute of background about my experience in this area. I'm an expert, when it comes to polypropylene materials, and plastics materials in general. I've helped 9000 women get settlements in this area in the USA, and I've spent hundreds of hours; I've read about four or 500 articles on this. So, this is not just an opinion based off the top of my head, this is an opinion based on decades of experience and a huge amount of specific research in this area.

PP is inherently unsuitable, and that is something - it's not an opinion, it's a scientific fact, because polypropylene is unstable.

It's a material that oxidises, just like a fresh apple would oxidise, and it loses strength in any situation where there's air. So, that could be in air, it could in water, and also in the body, and that's been proven.

It's not just an opinion, we know that polypropylene loses its strength and fails in the body, because it's oxidatively unstable. It has been absolutely proven by hundreds of scientific papers. It's also, based on other articles I've read, not suitable because it's not bio-compatible, and it causes inflammation and pain, and there's a huge amount of data on that as well. I have probably 300 articles on that. That's my opinion. It should never have been used, and it should have been obvious to anybody with any experience in plastics.

Julia Cumberlege: Right. Thank you very much for that. I will introduce the other people around the table. But before I do that, perhaps Dr Vladimir Iakovlev can start- I

Vladimir Iakovlev: Okay, my background is I'm a pathologist. So, I see the patients which are unhappy when the mesh is excised, and they are seeing me as a pathology specialist after complications. So, I always see the side of complications, I don't see the happy stories. I've been in mesh research for about six years. I've examined over 500 explant cases or explant specimens.. I've been involved in litigation as well, on the plaintiff's side. It's always been on the plaintiff's side.

What I do, is I examine the specimens, I try to determine what's the nature of the reason when the mesh is excised for complications. In over 95 per cent, the surgeon is correct. The reason which clinically is responsible for some complications like pain, is actually mesh. It's only in minority of cases, less than five per cent that I find some other foreign objects which were mistaken by the surgeon as mesh for example, staples, sutures, gauze material and so forth.

So far, over 500 cases, I have not found a natural disease, like a tumour, which would be responsible for complications. The complications are - can be split into large groups of pain, including dyspareunia, erosion, external erosion or exposure of the mesh, and internal erosion into the tissues inside.

To say suitable or not suitable, I will let your gynaecologists and other specialists decide if it's suitable or unsuitable. Because everything, I think, will boil down to risk to benefit ratio. The mesh itself does not behave as natural tissues. It is not accepted as native tissue. It triggers foreign body reaction, the same as a piece of glass or a bullet, or a piece of wood, or a wood splinter in

the tissue. There will be foreign body type inflammation, there will be scarring. The mesh is a foreign object, and a scar will contract inside and will tighten it.

It also behaves as a foreign object inside the tissue, and it can migrate, damaging tissues and other components like nerves or vessels. Can transmigrate to organs like the bladder or the rectum. So, the view which was sometimes described as it triggers minimal inflammation, or if accepted by compatible material - I don't see evidence that it behaves any differently than any other foreign body. Obviously, you can have some potential benefits from any object, physical structure or physical support of some sort.

But, at the same time, the same material will cause damage. I think it will all boil down to the point where benefit and risk ratios are assessed for the duration of implant in the body. Since these implants are permanent, this will be a life-long situation. So, what we have to do to decide if it's suitable versus unsuitable, is to compare long-term results of benefit and complication. Long-term, I don't mean four or five years. It may be only half of the complications will accumulate after four or five years.

Actually, what we've been doing lately, we've been analysing timing of the events of complications and timing it by excision, and about 50 per cent of complications accumulate within the first four or five years. Then it might take another 15 years, 10 to 15 years to accumulate another 50 per cent. Because sometimes the mesh is excised 20 and 30 years after implantation. In order to assess long-term risks and benefit ratio, the studies need to follow for 15 years or even longer.

That's a summary of my findings, or my understanding of the process.

Julia Cumberlege: Right. Well, thank you very much indeed for that. I'm going to now invite our two experts here from the United Kingdom to come in, and then I'm going to introduce the people around the table. So, Professor Vikram Khullar, are you there?

Vikram Khullar: Yes. I'm head of urogynaecology at Imperial College, and I - we've had an interest in - our first complication in mesh was nine years ago. We - certainly, our experience has been that with meshes which were used previously, where there were multfilament, or Teflon, these were rejected, and there was a very high rate of complications with them. With the polypropylene mesh, we are certainly seeing in patients' bodies that they are covered with fibrosis, and that…

Jan Willem Cohen Tervaert: Hello, this is Jan Willem Cohen Tervaert, sorry, I'm a little late. I had another meeting which was a little bit too long. Sorry for that.

Vikram Khullar: Okay. Basically, we would argue that a large number of patients do benefit from the mesh. I haven't had any - I have not given any evidence in relation to mesh complications, and therefore have not really played a role in those sort of discussions. We certainly do see some patients where they have problems with mesh implants and they have - but it's - we think that it is a human factor. It's something to do with the way the patients interact with the mesh. Thank you.

Julia Cumberlege: Right. Thank you very much for that. Dr Mark Slack, we've seen you before, and you've come and given us evidence. I wondered if there's anything you'd like to respond to what's been said so far?

Mark Slack: I'm really struggling to hear. I didn't hear - if you're asking me…

Julia Cumberlege: I was inviting Dr Mark Slack to say whether there are these views that you want to express or ones that you want to contradict, Although we've already taken oral evidence from you in the past. I wondered if there's anything you'd like to say now before I invite Dr Jan Willem Cohen Tervaert. So, Mark, would you like to say anything?

Mark Slack: Thank you. One of my concerns here, again, is we talk generically about mesh, and we fail to discriminate between the various subtypes and the categories. Just for the sake of the people who don't know me, I was very vociferously against the introduction of mesh in the 1990s, because I was very aware of the trouble people have had with mesh in the 1960s in Oxford. I then generated a bit of work in animals, and looking at the mesh types, to try and understand it better. I only personally ever used mesh in limited amounts clinically after the publication of the first completed randomised controlled trial.

As Vik said a few minutes ago, it is incorrect to put the constructs - different constructs of mesh into the same conversation, because they are clearly very different physical characteristics between monofilamentous large-core meshes and multifilamentous and small-core meshes. I published a categorisation of these.

They all induce a foreign body reaction, but of different intensities. A monofilamentous mesh has 10 white cells per high-power field, compared with collagen, for example, which people oppose which is 100 white cells per high-power field. Most of them settle down, and if you compare type 1 macrophages to type 2 you see deposition of fibrous tissue and incorporation in the vast majority,

but only a very small residual inflammatory response in the type 1 meshes. Whereas the type 2, 3, 4, 5, you get an ongoing increasing inflammatory response, which leads to a much higher rate of erosion.

Then comes your second problem. If a monofilamentous mesh erodes into the vagina, you see a bit of mesh, it can cause discomfort in intercourse, and it's relatively easy to deal with. If a multifilamentous mesh migrates into the vagina, it acts like a wick. It absorbs vaginal fluid up along its path, with subsequent abscess formation and fairly critical consequences. So, I think it's extremely important that we divide these in the first instance.

The second point when viewing the risks/benefits of mesh, is whether we're talking of vaginally implanted mesh, mesh implanted for incontinence, or abdominally implanted mesh. Again, we will see three completely different responses, which is supported in the world literature. Whereas, if you look at the abdominal implants of meshes, you'll see erosion rates somewhere in the vicinity of three to four per cent, and you'll see total explantation rates in the vicinity of two per thousand cases. That's published, and I have it in front of me.

You see a very low rate of complication in the retropubic meshes, and then you see a relatively high rate of complication in the transobturator meshes. Probably nothing to do with the mesh, that's due to the fact that the mesh was placed between five sets of adductor muscles in the thigh, which in anybody's books, is probably not a good thing to have done. So, we're trying to, again, have a relatively superficial conversation about mesh when we're putting them all into the same category.

As one of the earlier speakers said, we really have to think very carefully about risk benefits. If we are going to say that, for example, the mesh can't be used for a retropubic TVT type operation, then we have to compare it with the alternatives, which is an autologous fascial sling or a laparoscopic colposuspension, both of which almost certainly have higher complication rates. So, we are therefore making a decision that may have an impact on patients in a different way. I think that's very important.

In terms of vault-supporting procedures, we do know that the best long-term durable results obtained with an abdominal sacrocolpopexy, and again, if we ban it in that circumstance, then we have to realise that that's a much higher percentage of patients who will require repeat surgery, with all the inherent dangers that repeat surgery brings with it.

All along, when I gave evidence to the commission and to the hearing, I made it very clear that I had been very critical of mesh, the methods of introduction, and the people that have used it. But I have been hesitant to call for a total ban, because I suspect that we could cause more trouble than if we left it in limited use.

The final part of that, is we see clear differences in outcomes when the meshes were placed by surgeons with low experience compared with surgeons who have extensive experience. Therefore, there's definitely a factor there. The final difference, of course, is the patients in whom they are placed. We know that patients who are smokers or who are obese have a way higher complication rate than people who are fit and healthy. There are so many variables here, but if one looks at the total complication rate of meshes in the published literature, it is nothing as high as people have suggested in the lay press.

Vladimir Iakovlev: I just want to remind you that when these studies are published, and they give a number, we always have to look at follow-up time. Because we cannot compare studies of, for example, two or three years long with those which lasted for much longer, for 10 years. Because the complications will keep rising. Because study continues beyond 10 years, they will still keep rising. Not at the same rate, but they will be higher.

So, when you compare complication rates or risk benefit ratio, we have to compare apples to apples and oranges with oranges, and the definition will be for a long time. If the study is shorter, it has to be assumed that the complication rate will be higher if it was extended for the same length of time.

Julia Cumberlege: Can I just welcome you, Dr Jan Willem Cohen Tervaert. You're from Canada.

Jan Willem Cohen Tervaert: Thank you very much.

Julia Cumberlege: . Can I just recap who's in this room, who's in this conversation? So, first of all…

Jan Willem Cohen Tervaert: Yes, please.

Julia Cumberlege: We've had Dr Chris DeArmitt from the USA. Dr Vladimir Iakovlev. We've got Dr Jan Willem Cohen Tervaert, who has just spoken. We've got Professor Vikram Khullar, who has also spoken, and Dr Mark Slack. So, these are the experts that we have invited to come and tell us your views. I want to thank you so much for coming and joining this conversation.

Now, I want to say who's around in the room here. So, I'm Julia Cumberlege, and I've been invited by the Secretary of State to chair this review. On my left is Dr Cyril Chantler, and Professor Cyril Chantler, no less. Cyril, would you just like to introduce yourself a little bit, or comment on some of the comments, so people hear your voice and they know who you are.

Cyril Chantler: Right, well, can I add my thanks to yours, because we're really grateful to you for giving up time. I know Vikram Khullar, and I know Mark Slack, but I don't know the other people on the call. But again, I say, we're very grateful to you. Thank you.

Julia Cumberlege: Then we also - the third member of the panel, and it is the panel who are going to make the decisions and take the responsibility for writing the review, opposite me sitting in this room is Simon Whale, and Simon, perhaps you could just say a word about yourself.

Simon Whale: Yes, I'm Simon Whale, hello, everyone, thank you again for joining this call. It's very important to us and very useful to have you on the call. I'm the third member of the panel as Baroness Cumberlege has said, and I also lead on the communications of the review with stakeholders, including patient groups and all the other stakeholders we have to interact with.

Julia Cumberlege: Thank you, Simon. Dr Valerie Brasse, who is our secretary. Valerie.

Valerie Brasse: Hello, I've certainly met Mark Slack, and I've certainly met Vikram Khullar, it's lovely to speak to you again. As I say, my job really is to make sure that the review runs as smoothly as possible, and I'm sort of the interface between the outside world and the review panel.

Julia Cumberlege: Thank you, Valerie. Dr Sonia MacLeod, who is our principal researcher. Sonia.

Sonia MacLeod: Hello, as Julia said, I'm the principal researcher.

Julia Cumberlege: Right. Thanks very much, indeed. Now, we've heard your initial thoughts. Obviously, this conversation needs to go on. Because we are actually working to fairly minimal technology at the moment, I'm just wondering if you would be kind enough, before you speak, just to say who you are. That would be very helpful, till we really recognise your voices. But I'm wondering if Professor Cyril Chantler from our side - Cyril, is there anything further you'd like to say regarding the conversation today?

Cyril Chantler: No, we have a series of other questions which we prepared, so I think it would be quite useful if we could go through those, and see how far along we can get.

Julia Cumberlege: Right, so, would you like to ask a question?

Cyril Chantler: Yes. It rather comes from the conversation that we had last week with Professor Khullar. Vikram, you said that meshes always shrink, and they shrink - the tapes in one dimension, obviously, if they are a patch, then they shrink in two dimensions. They are more likely to shrink if they are in contact with the air, or if they get infected. I wondered what the general view was about shrinkage?

Cyril Chantler: Dr DeArmitt, what do you think about that?

Chris DeArmitt: The mesh itself does not shrink. The mesh creates a response in the body, polypropylene does not change its dimensions. What happens is that it creates a response in the body, that forms scar tissue, as one of your experts just said, and the scar tissue is what's creating the shrinkage. But the material itself is not shrinking. What happens to the material is it oxidises, it loses strength, and it fails.

I want to make an important point here. We were saying that there are different types of mesh and we need to consider the differences. But we really don't. Polypropylene is completely unstable and will only last two to four years, according to every expert. Professor [redacted], all the top experts in the world have agreed that polypropylene mesh will last two to four years in the body. It will degrade, lose all of its strength and break into pieces.

It doesn't matter whether you're talking about a monofilament or a multifilament, et cetera. It's just an unsuitable material. You don't even have to get into those details. You don't even have to talk about whether it's biocompatible, although it isn't biocompatible. It's still an unsuitable material, and that's absolutely clear. There's hundreds of thousands of people with class action lawsuits, saying that they're having problems. So, to say that it's a problem that's down to a couple of percent, or insignificant, I think, is missing the point.

Mark Slack: Can I ask a question? It is a foreign body, and you're saying in response to oxidation. But in fact, I run a mesh removal centre, and we've done significant amounts of revision surgeries. It is not our experience to find that it's broken into parts when we remove it at six, seven, eight or nine years. So, that's clinically not what we've seen, and the clinical response of a lot of the patients with these operations last way beyond that. So, I think we've got to be a little bit careful not to be too dogmatic about that.

We also have the example of the hernia meshes, where there are in the United States alone, one million placed per annum, and have been since the 1990s, since about 1994. So, if we only had

a one per cent complication of polypropylene hernias, we would have had a million cases a year over about 20 years. I suspect we would have seen hundreds of thousands of patients with these complications. I'm just asking for us all to be a little bit cautious with our dogma when we make these statements.

Vikram Khullar: Professor Khullar. can I just say, I absolutely agree. We have - we run a mesh centre in London, and we remove around 70 meshes a year. We have certainly removed meshes which have been in place for 12 years, encased in scar tissue, and it does not fall apart. So, it has not been our clinical impression.

Cyril Chantler: Do you - Vikram, you told us that in your opinion it does shrink, however. It's not just a question that it gets fibrosed, it actually shrinks?

Vikram Khullar: It does shrink, and I'm sure the shrinkage is due to the scar tissue. So, to be accurate, if there's scarring around the mesh, it causes shrinkage, and we noticed that this shrinkage occurs within two weeks of the insertion of the tape, and then it becomes fixed. It must be the scar tissue causing it.

[Over speaking]

Mark Slack: The natural tissue operation we see between 20 to 40 per cent shrinkage of the cross-sectional area of the scar that you have operated on.

…

Chris DeArmitt: The point I was trying to make is that polypropylene is unstable. We know that it loses strength in the body; it's been measured. Eventually, it will fragment and fall to pieces. There is no chance that most of the polypropylene used today is stable or ever should have been implanted.

One of the surgeons made a great point - one of the experts made a great point, that you need alternatives, because these patients need an operation. There are other polymers which have been proven to be stable in the body for - much, much more stable than polypropylene. So, there are viable alternatives. There's no need to say that we need to carry on with polypropylene because there are no other options. Because there are other proven commercial options on the market right now.

Cyril Chantler: Could you tell us what they are?

Julia Cumberlege: Could you say a bit more about what are the other polymers?

Chris DeArmitt: Mesh made of PVDF has been on the market for years, if not decades, and it's proven to be more stable, far more stable than polypropylene.

Cyril Chantler: What do others think about that?

Vladimir Iakovlev: Vladimir Iakovlev. I see what happens with the tissue, I see what happens with the polymer itself. Issue number one, shrinkage. Yes, it is correct that shrinkage is caused by scar tissue. The polypropylene in itself doesn't shrink. What happens, the fibres of the mesh are being pulled together by scar tissue inside the mesh and outside the mesh. The initial response of scar tissue, or formation of scar tissue happens within the first few weeks. Three to four weeks, somewhere in there. So, the initial contraction will happen within first couple of weeks, up to four weeks.

Then, if there is any extra damage, if there is inflammation, and there is always inflammation, then the scar tissue can be sort of slow growing and there can be additional contractions, but at a minor degree.

Regarding polypropylene degradation, what happens, what I see - the degradation starts on the surface, so it's not the entire fibre which degrade, it's the surface. I call it in analogy with the tree bark, like a bark layer on the surface. The core of the material stays untouched, unoxidized, non-degraded. But yes, it does change over time.

The implants which were explanted, removed 10 years and longer, they show much thicker degradation layer. That degradation layer becomes brittle, and then it can flake off. But usually, those fragments are sort of staying around the fibre itself. They don't migrate, unless they are mechanically disturbed.

I see these particles in tissue - of degraded layer left in the area after mesh excision. For example, if there is a repeat excision, then I can see the remnants or sort of contaminants of degradation material in the scar tissue. That's what I see in the microscope.

Cyril Chantler: Thank you very much.

Chris DeArmitt: Thank you for describing that. This is important. You have a rope, that's your fibre, okay? It has a certain strength. As you're degrading the surface, that rope is getting thinner and thinner and thinner and losing strength. So, it's going to fail. That's been measured. We know that that polymer - even prolene mesh loses 30 per cent strength in a very low amount of time, whereas PVDF mesh does not.

So, this degradation does start at the surface. It's the same for polypropylene pipes or any other - or a garden chair left out in the garden. Any polymer piece made of PP starts to degrade at the surface, and that gradually works its way inside, and then your

effective diameter of your fibre that can bear a load is becoming less and less and less. So, the product is no longer able to perform its function. That was a great description, thank you.

[Over speaking]

Mark Slack: I agree it was a good description, but I can't agree with your interpretation. You're talking a bit about pipes which are exposed both to sun and to air, which is not the case in the human implantation. Number two, we have 20 years' data for some of these operations, [unclear]. In perspective of randomised controlled trials. I think it's a bit premature to - I am also - I know the characteristics of PVDF very well. I think it would be premature, considering the paucity of data on PVDF, to make a conclusion that it is superior or stable.

Cyril Chantler: Thank you.

Chris DeArmitt: We know that it retains its strength better, and that's a fact.

Mark Slack: Do you need 100 per cent strength? The polypropylene strength is way in excess of what we actually need to support vaginal tissues, which we also know. Nothing's ideal. Certainly, would I prefer to have something that was different from it, of course I would.

However, what I'm saying, is when we are making this judgement, I really want everybody to be very careful to remember what we are committing to. If we ban this mesh completely, it means that patients can only have natural tissue operations, probably, until we have the data, and those have suboptimal outcomes, and they have complications associated with them, and they require repeat surgery. I think I just want everybody to always be cautious about what the alternative is.

There's a huge amount - I was the person who fought against mesh almost - before this subject ever became an issue, I was lecturing against mesh in the 1990s. But I waited for the randomised controlled trials, I saw the benefits that it gave in certain areas. I restrict that to TVT retropubic sacrocolpoplexy and sacrohysteropexy. I don't believe in the trans vaginal ones, and I don't believe in the transobturator ones.

If we remove those operations, we're committing patients to operations with poor outcomes, high complication rates. We won't get away from the complications - for example, pain. Some of the randomised controlled trials of mesh operations versus non-mesh have higher pain scores in the non-mesh operations. So, the pain is another very, very complicated area.

I'm just asking everybody to be very cautious and to make sure that their level of expertise is such that they can make an honest judgement whether or not we are doing the right thing for a patient group.

Julia Cumberlege: Thank you very much for that. Of course, of course we want to do the right for a patient. Can I just say, Dr Slack, at the last oral hearing, you said that the mesh becomes brittle when it's exposed to oxygen through erosion. Is that still your case? Do you still believe that that is what happens if the mesh is exposed to oxygen? It becomes very brittle?

Vladimir Iakovlev: Degradation is not related to erosion. The degradation layer forms on all fibres and erosions are deeper on meshes which have not been eroded anywhere. It's just properties of the material itself in contact with the tissues. It is not related to erosion or exposure to oxygen.

Chris DeArmitt: That's correct.

Vladimir Iakovlev: The oxygen is in tissues. It doesn't have to be exposed to air, that's a more correct definition.

Chris DeArmitt: That's correct from a materials point of view. Polypropylene degrades in air, in water and anywhere where there's oxygen, which - there is oxygen dissolved in the blood and the tissues in the body. So, polypropylene will degrade [unclear] the body.

Julia Cumberlege: What about the…

Vladimir Iakovlev: I just want to draw a little bit of attention towards physical properties of non-degraded material as well. Because if we talk about degradation, one of the major points is that if the implant changes over time, and the - it was implanted for life, it shouldn't change, in my opinion. If it changes, it means that its properties will be different over time. If - for example, the patient was younger, 30, 40 years, they may live with the device for 30, 40 or 50 years. So, if the material changes over time, it may have to be excised at one point. So, it should be stable.

Mark Slack: Ladies and gentlemen, all implants undergo changes. Hips undergo changes, heart valves undergo changes. It isn't perfect material. But the alternative is to do nothing.

Chris DeArmitt: That's not true, there are proven mesh alternatives.

[Over speaking]

Vikram Khullar: Sorry, right at the beginning, when the polypropylene tape appeared, the suburethal tape, we specifically waited for the five-year data, because our previous experience through the '70s and '80s, was that a number of materials had been used in the same

way, and there were very high complication rates, and they occurred within five years. We did not see those, such high rates with polypropylene.

So, I'm not sure that there is going to be a doomsday scenario where something terribly big happens. Because the polypropylene mesh always appeared to be encased in this fibrosis, in the scar tissue. The scar tissue is almost holding the material together. In a way, the material itself becomes irrelevant, because it's the scar tissue which probably leads to the supportive role of the mesh. That's probably the reason why even though there's 17 to 18 years of data now, we don't see a problem of failure of the material or the operation in those patients.

Julia Cumberlege: Can I just return back to the polymers, the new polymers. Are they more durable? Are they less likely to break down because of the body heat or the leeching of chemicals and things like that?

Chris DeArmitt: Yes, the PVDF mesh contains zero additives and it is much more oxidatively stable. So, they've tested it in the body, they've measured the strength over time, and polypropylene loses substantial strength. This is not just one article, polypropylene has been shown for years to lose strength and degrade in the body, whereas a PVDF mesh does not.

Julia Cumberlege: Right. Is there a list of these polymers that are more successful?

Chris DeArmitt: There are other polymers used. There's DET and there's PET, PTFE, but I would not give a conclusion about whether they're overall more suitable than polypropylene, because they also have disadvantages. Of all the articles I've read, the PVDF mesh is - gives the best results. I have no conflict of interest; I'm doing this unpaid just because I care about the health of women and men around the world who are getting mesh implants.

Julia Cumberlege: Right, well, thank you for that. Cyril, do you want to come in, and then Simon.

Cyril Chantler: Yes. I think it would be useful now if you can, to move the conversation on a little bit. One of the concerns that has been expressed to us by women across the country is that they develop systemic symptoms which they ascribe to their bodies reacting to the implant. We know it creates scarring locally and an inflammatory action, but the question is, do you develop a systemic inflammatory response, and perhaps, Vik, you could - Vik Khullar, you could start, because you've talked about this when we met last week. Then maybe, Dr Jan Willem Cohen Tervaert could come it, because I understand this is very much your area of research. If we could start, Vik, with you, and then go over to Dr Tervaert, please.

Vikram Khullar: Yes. We certainly have been investigating these patients who have meshes and mesh reaction. We have found that they have certainly an abnormal microbiome, and those are the patients who are more likely to suffer pain. There are certainly, now publications discussing that cytokines have been found within the mesh itself, and we have identified a group - a population of about 12% of them who have an abnormal immune reaction to very low levels of bacteria, which can be with an implant.

Because it's related to the innate immune system, it does not appear as a rise in CRP or other systemic markers of inflammation. But locally, it will cause pain and it's in the same group of people who suffer from fibromyalgia. We seem to have a group who probably should not have - or who would adversely react to implants.

Cyril Chantler: Thank you. Dr Tervaert?

Jan Willem Cohen Tervaert: Sorry, I have been disconnected, so I missed some part of the discussions. I'm sorry for that. My name is Jan Willem Cohen Tervaert, I'm a professor of medicine and immunology at the University of Maastricht, but currently I'm director of rheumatology in Edmonton in Canada. I have a long-term experience in foreign-body induced inflammation, and especially causing auto-immune diseases. We work with different implants, silicone breast implants, hip implants, mesh implants and others. So, I see mostly patients who suffer a lot.

For instance, Friday, one of my ladies came and she was very happy. Her mesh could be completely removed. I saw her three months ago coming in a wheelchair with very severe muscle weakness, positive antibodies for myositis. Now she came in smiling and saying the mesh was gone, and her heart and lung disease is cured.

That's just an example of the kind of patients that I see. So, all mesh, at least all polypropylene mesh, induce an inflammatory reaction as soon as they are exposed to a human body. Of course, inflammatory reaction is not the same in all the patients. So, some patients have an exaggerated immune response, and others seem to tolerate these meshes quite well, with respect to the immune response.

So, there's certain risk factors that we clearly have demonstrated in other implants, but also, these seem to be true for the mesh implants. Which is that if the patient has a strong allergic constitution, that they will have more chance to develop also systemic immune problems after implantation.

What are these complaints that you see? Generally, these patients do have severe fatigue, so that if they wake up, they are already very tired, and there's clear post-exertional malaise in these patients, so they fulfil the criteria for chronic fatigue syndrome. In addition, they have joint pains and muscle pain, which is widespread. Therefore, they fulfil the criteria of fibromyalgia.

Strange enough, most of these patients did develop these diseases after implantation, and did not have it before, although some had it before already, and then it is increasingly severe. Nearly all have quite severe cognitive impairment, meaning that they have word-finding problems, they have kind of Alzheimer light and concentration problems, which generally ameliorates after explantation.

Most of them also have pyrexia, feverish feelings, nearly all of them have very severe sicca symptoms, dry eyes, dry mouth. Then in addition, some have those more typical neurological symptoms such as a stroke at a young age without the classic features that we see in a stroke or cardiovascular disease, or multiple sclerosis-like symptoms.

For mesh, we don't know whether there is an increased risk of immunodeficiencies and autoimmune diseases, but in my experience, and that's not evidence-based, there is an important amount of patients, up to 40 per cent, who develop autoimmune diseases, and will develop immune deficiencies. That's a similar scenario that we see in other implant induced diseases.

The question, though, is how often does this occur? We have no clue at present. I've seen many patients nowadays, I would say around 100 patients, and that doesn’t say anything, because there are hundreds of patients been mesh implanted. The crucial finding, however, there is always immune response to polypropylene, and if there have been very strong responses, that means that there might be induction of mistakes of the immune system. That means autoimmune diseases, and it can also result in immunodeficiencies.

Cyril Chantler: Can I ask you, and then I would like the other people on the call to come in and comment, please, but are there any bio markers, any diagnostic tests that are available? We know that - from what I learned that there are rarely significant rises in C-reactive protein, or sedimentation rates, or cytokine production. Are there any other biomarkers - we know about - aminoxidase, for instance?

Jan Willem Cohen Tervaert: Sorry, generally, the C-reactive protein is normal, so what you see quite often, is that there is immunodeficiency, so

IgG levels and/or IgG subclass levels are decreased. Many of these patients do have elevated angiotensin-converting enzyme levels, and soluble acidic CD20 so the soluble interleukine 2 receptor which is elevated.

There is quite often also extremely high, elevated total IgG levels. But there's no specific marker, until now. If you do explantation, you clearly see there's granulomatous inflammation, so the whole picture is the picture of the patient with a sarcoid-like disease. Of course, we know that with sarcoid, many of these symptoms occurs, both with sarcoid, soluble interleukine receptor 2 levels are elevated, and also in sarcoid, sometimes steroids work very well, and that's also the case in these patients. If you give them high-dose immunosuppressant, which is of course not what we want, because it's persistent inflammation, but they temporarily are then better.

Cyril Chantler: Could I ask Professor Khullar, does that in any way relate to the work you've been doing on histamine?

Vikram Khullar: The patients who we see are very similar. We found that 40 per cent of them have IgG subclass deficiencies, and 40 per cent of them have a mannose-binding lectin deficiency, where in the population, it's around five to 10 per cent. They also will complain of headache, fatigue, and they will - and we get similar rate - around 5 per cent who will have antinuclear antibodies, but they will often have symptoms which are suggestive of sicca-like syndrome. Dry eyes, dry mouth. So, yes, they are exactly the same patients.

Cyril Chantler: Thank you. Can I ask Dr Slack, have you - Mark, have you come across any of these?

Mark Slack: Yes, I mean, we did some work in a different context on the microbiome, and we only saw alterations in the microbiome when it was a multifilamentous mesh that has eroded through into the vagina, well not eroded, in that case it was cervical cerclage it was left in the vagina and had absorbed the vaginal secretions and altered the microbiome of the vagina. We published that in *Science.* I'm not convinced that ordinary polypropylene monofilamentous really adjust - it's hard to explain the mechanism.

The question I'd ask everybody, fibromyalgia affects three to six per cent of the world's population on current estimates. What percentage of those have meshes in them? Then we've got a hell of a lot of people who have had meshes put in, as I said, just hernias alone, a million a year. What percentage of them have

fibromyalgia? I think I'm seeing some huge generalisations being made here on a very, very tentative evidence base.

I'm just asking for us to be scientific and honest and a little bit cautious about what we - I mean, I find it curious that in some ways I'm defending these meshes, then I lived through the years when we had nothing but natural tissue operations, and the really considerable consequences of those operations, the poor outcomes and the impacts on quality of life.

I'm just saying to everybody, let's just be a little bit cautious here. I hear the stories about the - also a lot of these cases that you're talking about, the collagen and everything else, the confidence intervals of normality are quite wide, and the variations within the normal population are quite wide. I'm not sure how we are drawing conclusions - your expert actually said this is not an evidence-based argument. If we select out affected people, we are seeing a biased group.

Let me go back to America. One million hernia implants per annum in America. I use it as an example because I then [unclear] that group We're not seeing even 100,000 hernia implants complaining of difficulties per annum in the US.

Chris DeArmitt: But there is a class action litigation on hernia implants in the US.

Mark Slack: Your class action litigations are in every aspect of medicine where there's a pharmaceutical company involved, because there's money to be made. There's more dishonesty going on in class actions in America than one can actually believe. If you read the New York Times articles, they will tell you how hedge funds are encouraging people to have their - doctors working for hedge funds are encouraging people to have their meshes removed. Because once their mesh has been removed, they are now injured, and they can therefore enter into the class action. Once they've entered into the class action, the lawyers wait about a year, then say, this is taking for ever, we'll give you 50,000 now but you sign over your rights to us.

Julia Cumberlege: I'm sure…

Mark Slack: Evidence based from the literature.

Julia Cumberlege: I'm sure you would agree that when we are doing operations, some of them are quite novel, others are very well established. But one would want to ensure that they are as safe as possible. That is why we introduced the pause, because we were concerned, having listened to thousands of women, we were concerned that what was being done at the moment could have been done a great deal safer.

That is why we are anxious about the precautionary principle of first, do no harm. So, what we are trying to do is to ensure that for the future, whatever is done for SUIs or pelvic floors or all that area, we want it to be as safe as possible.

Now, I'm going to move on to Simon Whale, who is the other member of our panel. Simon.

Simon Whale: Can I just slightly change the subject with a further question, I think it might be our final question, which is - I'm conscious that we've got an international perspective amongst the participants on the call at the moment. You've had, between you, exposure to European Union and US regulatory regimes. My question is whether there's anything that you think should be added to either the premarket or the post market testing in the UK for implantable devices to achieve safer outcomes? Can I start with…

Chris DeArmitt: Yes, I'd like to make a comment, this is…

Simon Whale: Sorry, go on.

Chris DeArmitt: I was going to say something, yes. So, the polypropylene mesh has not been tested properly. I mean, the scientists for the manufacturers themselves have said that this stuff was rushed to market without proper long-term testing, which I would expect to see - I've worked for [redacted], and we test the heck out of everything. We do extreme testing for dishwashers, washing machines, vacuum cleaners, and even that level of testing for a regular household appliance has not been done on the material used for this mesh. It's absolutely shocking, and I've never seen anything like it.

So, yes, I think that there is standard testing that should be done to test whether this material is stable enough. We've had world experts, the top experts weigh in, and we know from the work that's been done already that it isn't stable. But the onus is on the manufacturer to show that this material is stable and will last a lifetime of the patient, and that work has not been done.

So, at a minimum, they would have to write - in fact, polypropylene says on the safety data sheet, not to be used inside the body, because it's not suitable. It's a safety warning which is given out to everybody. Do not use polypropylene in the body, this is an unsuitable material. That was ignored, and yet, they didn't go on to do the testing to see whether the appropriate additives were put in the polypropylene to try to protect it.

So, yes, there should be a warning on the material now, saying this is made of one of the world's least stable polymers, and we have no conclusive evidence that this will be stable for the life of

the patient. That's the current state of the situation. Until they've shown that evidence, and done that testing or reformulated their material, it shouldn't be on the market.

In America, they've gone even further. They ran out of genuine polypropylene, [redacted]. So, we have to be very careful. This is a billion-dollar industry, these people are paying off experts to lie, and they're importing counterfeit material and implanting it into women because they want to keep their profits going.

This is a high-stakes game, and many people are not being candid with their expert opinions. That's what I see in the US. So, we have to be very careful about that.

Jan Willem Cohen Tervaert: May I add, you all probably know the scandal of the fruit wrapping that was approved for surgical implant as a mesh. That was the Dutch television *Radar* program. They were allowed to get approval for the mandarin, just from supermarket.

Chris DeArmitt: That was a documentary where a Johnson and Johnson executive admitted that they had tested the mesh, found that it was - had massive problems, and marketed it anyway. The way that they did that, according to the documentary, was to pay [redacted].

So, I do highly recommend that people watch that *Radar* documentary on - you can find it on YouTube, or I can send you a link if you haven't seen it. [https://youtu.be/lBxj4h8C36M]

Mark Slack: May I make a comment? [redacted]. That documentary is far from honest itself, and it's far from accurate.

However, I would entirely agree with you that the way they brought the meshes to market was irresponsible. They had not done the basic testing required in animals prior to implantation in humans. Some of the meshes, however, did undergo extensive clinical trials, using randomised controlled trials with up to eight years of follow up.

I personally am not convinced that randomised controlled trial is sufficiently rigorous for an implant, because they are usually too

small to identify remote complications, and too small to identify infrequently occurring complications.

My recommendation would be that any implantable mesh, or any implantable substance undergoes appropriate animal testing, followed by, once introduction, by compulsory registries, which is the one mechanism which will clearly identify a problem early.

Vladimir Iakovlev: May I have a comment? Vladimir Iakovlev. I completely agree with registries. Approval of implantable devices and long-term drugs has to be a multi-step procedure. First, in vitro experiments, then in animal experiments, then when the devices or drugs are introduced into humans, there should be a small cohort followed for a few years, but then, even after they clear it for sale, they have to be registered.

Every single device or long-term drug has to be registered and monitored. Therefore, we can flag devices or drugs at early stage, when there is real-time monitoring. Because the implants are lifelong, and the complications may keep rising for 10, 15 years, even longer. Therefore, we can identify those which are likely to be problematic long-term much earlier. Not to wait until the disaster comes like we hear it now.

Vikram Khullar: Professor Khullar. I think, in addition, the most important thing when these materials have been implanted, often the studies will only look at - for example, with the suburethral tapes, bladder dysfunction, and organ-specific complications. Really, any reporting system, and certainly, when looking at studies, they should be looking for other problems, such as pain or autoimmune conditions. Things which may not have been conceived of by the implanter. So that even prior to the material going on sale to the general population, other complications will be - people will be trying to look for these other complications, so that problems won't occur once they are released to the public.

Then in any registration scheme, or reporting scheme, the same as drugs, that even a complication which does not appear to be related to the implant is still reported. Because often, the surgeons who have put the implant in will only deal with their organ. Sadly, some of the complications may not have anything to do with - they may be something to do with other organs, which don't appear to be related. Only by looking at a population do we realise there is a significant group who are having complications which were not predicted.

Julia Cumberlege: Right. Can I draw this now, to a close, and to thank you once again for coming onto this conversation from all parts of the world. We are very, very grateful to you. We will obviously, record this,

we're going to listen very carefully to what you've been telling us. We hope to publish our report sometime towards the end of the year or into the next year. So, thank you, it's been a very valuable input into what we've been trying to do. I want to thank you very much indeed, for all your help. Thank you.

Vikram Khullar: Thank you.

Mark Slack: Thank you very much.

Vladimir Iakovlev: May I add a comment? I think it might be better to collect information in written format. For example, if a list of questions was generated and all experts gave answers for specific questions, then you can identify areas of agreement and disagreement, and then the areas of disagreement can be then studied further, or discussed further.

Julia Cumberlege: Yes, thank you very much for that suggestion. We'll ensure we'll follow through with it. Thank you. So, if I could say, for us it's good night, it might be good morning wherever you are, I don't know, but it's been a very useful conversation. Thank you very much.

Chris DeArmitt: Thanks for protecting the public, it's an important job, we appreciate it, thank you.

END OF TRANSCRIPT

Dr Jan Willem Cohen Tervaert

Question 1:

Our patient groups have said to us that they feel synthetic mesh is unsuitable for long term insertion.

What are your views on this for the use of polypropylene mesh

- for stress urinary incontinence?
- for pelvic organ prolapse?

As mentioned by me during the telecon, PP mesh can induce a systemic inflammatory disease.

Questions are how frequently this adverse effect occurs ? And who will get this adverse effect ?

As long as we do not have good figures regarding these issues, I think that we should conclude that it is not safeto use PP mesh and that these PP meshes should only be used when other possibilities are excluded (with appropriate information to the patient that these complications may occur and after patient consent).

Is there such a thing as medical grade polypropylene? If so what is it?

All PP will stimulate the immune system; research to limit this activation is important.

Question 2:

We are interested in understanding the physical properties of mesh once it has been inserted, including:

- shrinkage,
- degradation,
- leeching of chemicals, and
- breakdown cause by body heat

When the immune system is activated, several changes to the mesh might occur resulting in above mentioned complications

Question 3:

What are your views on whether mesh degrades *in vivo*, and if so, how does it do so and what causes this?

When the immune system is activated, several changes to the mesh might occur resulting in above mentioned complications

Question 4:

Is there any consensus on ways to identify women for whom mesh is likely to be less successful?

For example, physical characteristics, immunological responses, vaginal microbiomes.

From the literature and from my study, it appears that women with pre-existing allergies and/or autoimmune diseases have an increased risk to develop systemic inflammation (called "ASIA")

Question 5:

We have an international perspective here, with exposure to the EU and the US regulatory regimes, is there anything that you think should be added to either the pre-market or the post-market testing for implantable devices?

As is true for new drugs coming to market, devices should undergo the same process of extensive testing in RCTs before coming to market

Dr Chris DeArmitt

Question 1:
Our patient groups have said to us that they feel synthetic mesh is unsuitable for long term insertion.
What are your views on this for the use of polypropylene mesh

- **for stress urinary incontinence?**
- **for pelvic organ prolapse?**

Is there such a thing as medical grade polypropylene? If so what is it?

Polypropylene mesh is totally unsuitable for long-term insertion in the body for two reasons. Firstly, PP is a very unstable polymer which degrades and loses strength rapidly in the body. The instability of PP is a scientific fact, like gravity. Secondly, PP creates an immune response leading to chronic inflammation and pain.

The safety datasheet for PP specifically prohibits its use in the body for long-term implants. I know from my experience in the plastics industry that so-called medical grades have no special properties. They are standard plastics renamed and sold at a premium. No matter what name it is sold under, there is no polypropylene on the market recommended for or suitable for long-term implantation.

Question 2:
We are interested in understanding the physical properties of mesh once it has been inserted, including:

- **shrinkage,**
- **degradation,**
- **leeching of chemicals, and**
- **breakdown cause by body heat**

The PP mesh material itself does not shrink, but it does cause the tissue around it to scar and shrink. That is the cause of the observed shrinkage.

PP oxidizes and degrades losing strength and its ability to perform its intended function. This has been well-known for several decades. PP is not stable whenever oxygen is present and it is present in the body. Furthermore, the body attacks the PP using radicals, which are the nemesis of PP.

Polypropylene contains chemical lubricants and stabilizers that are known to leach out of the PP and will enter the bloodstream. My understanding is that the stabilizers are not approved for use in the body, which is a concern despite the fact that their concentration is rather low.

The degradation and weakening of PP is accelerated by oxygen, heat, UV light. As a rule of thumb, it will degrades twice as fast for every 10°C temperature rise

meaning that mesh will degrade 3-4x faster at body temperature than it will at room temperature. Details are in the report I provided some months ago.

https://slingthemesh.files.wordpress.com/2018/05/phantom-plastics-mostyn-law-pp-mesh-design-report-final-cd-2018.pdf

PP degrades faster the thinner it is because the stabilizers are easily washed out of thin specimens. The PP mesh is very thin, which is a problem.

PP degrades faster in water than in air because the water washed out the stabilizers. Clearly, this is an issue because the body is composed largely of water.

Question 3:
What are your views on whether mesh degrades *in vivo*, and if so, how does it do so and what causes this?

There is no question we know for a fact that PP degrades in vivo. That has been measured and proven. The PP oxidizes, cracks and severely loses strength. Details are in the report I provided. There are other commercial mesh materials that do not degrade in the body. PVDF is the best example: https://en.dyna-mesh.com

Question 4:
Is there any consensus on ways to identify women for whom mesh is likely to be less successful?
For example, physical characteristics, immunological responses, vaginal microbiomes.

This question is outside my expert area.

Question 5:
We have an international perspective here, with exposure to the EU and the US regulatory regimes, is there anything that you think should be added to either the pre-market or the post-market testing for implantable devices?

The PP mesh was not properly tested. It was launched without even the level of testing I would expect for plastic used in a vacuum cleaner, refrigerator, car or similar consumer device. The product should have been exposed to proper long-term testing to make sure it is stable for decades as required by the application. Experiments show that the mesh can saw through tissue and that should have been checked before launch. This sawing action has been reported to cause women extreme pain.

It appears these products were not accidentally launched without proper testing. At least one manufacturer has testified that they were fully aware of all the problems and launched the PP mesh anyway.

[redacted]

[redacted].
What did Johnson & Johnson know? RADAR (AVROTROS) | English substitles
Watch the video here - https://youtu.be/lBxj4h8C36M

Dr DeArmitt also shared the following with the Review:

I have read over 400 articles on mesh for vaginal and hernia repair.

On the call today, at least one expert appeared to be claiming that mesh complications were around 1 % and that if we ban mesh there are no alternatives. Both of those statements are demonstrably incorrect according to the published literature. You are being mislead. Complications are relatively low only if you look at very short term outcomes (e.g. 1 year or less). As another expert correctly stated, the important numbers are complications after, 10, 20 and 30 years and we know that number climbs substantially. If you would like a short summary of the actual evidence, I can prepare one so that you can make an informed opinion. Here are just a few studies (attached).

Long-term Outcomes Following Abdominal Sacrocolpopexy for Pelvic Organ Prolapse

"Results of 215 women enrolled in the extended CARE study, 104 had undergone abdominal sacrocolpopexy plus Burch urethropexy and 111 had undergone abdominal sacrocolpopexy alone. Pelvic organ prolapse and urinary incontinence failure rates gradually increased during 7 years of follow-up. Probability of mesh erosion at 7 years (estimated by the Kaplan-Meier method) was **10.5%** (95% CI, 6.8% to 16.1%)."

One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse

"Objective and subjective improvement is seen after vaginal prolapse repair with or without mesh. However, mesh resulted in a higher reoperation rate and did not improve 1-year cure."

Use and risks of surgical mesh for pelvic organ prolapse surgery in women in New York state: population based cohort study

"After propensity score matching, patients who received the surgery with mesh had a higher chance of having a reintervention within one year (mesh 3.3% v no mesh 2.2%" Note, this was a 90 day - 1 year study, which therefore showed lower rates.

During the call, I mentioned PVDF as an alternative to PP. Multiple studies have shown that PVDF is very stable and contains no additives. Here is one graph showing Prolene PP losing over 40% strength in the body after just 7 years whereas the PVDF does not. I have attached the full article. PVDF is a proven, commercial alternative to PP that does not have the same drawbacks. See: https://en.dyna-mesh.com

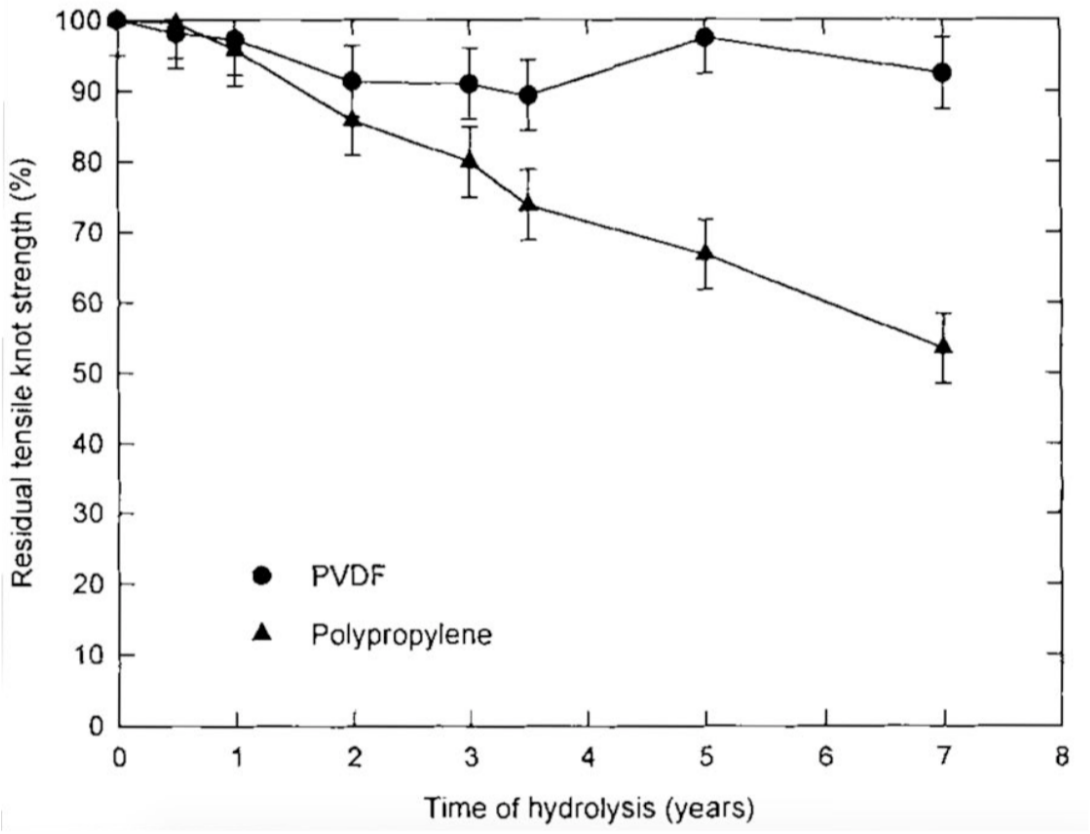

Figure 4 PP Sutures lost 45% of their strength in 7 years implanted in the body[7]

This video shows a mesh manufacturer testifying that the mesh causes problems and they launched the mesh knowing all the problems:

https://youtu.be/lBxj4h8C36M

Attached papers

- Sokol, AI, Iglesia, CB, Kudish, BI et al. One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse. American Journal of Obstetrics & Gynecology. 2012; 206(1): 86.e1 - 86.e9 doi: 10.1016/j.ajog.2011.08.003

- Nygaard, I, Brubaker, L, Zyczynski, HM et al. Long-term outcomes following abdominal sacrocolpopexy for pelvic organ prolapse. JAMA. 2013; 309(19):2016-24. doi: 10.1001/jama.2013.4919.
- Chugtai, B, Mao, J, Buck, J et al. Use and risks of surgical mesh for pelvic organ prolapse surgery in women in New York state: population based cohort study. BMJ. 2015; 350:h2685. doi: 10.1136/bmj.h2685.
- Laroche, G, Marois, Y, Schwarz, E et al. Polyvinylidene fluoride monofilament sutures: can they be used safely for long-term anastomoses in the thoracic aorta? Artificial Organs. 1995; 19(11):1190-9. Doi: 10.1111/j.1525-1594.1995.tb02282.x

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Review Team

Independent Medicines and Medical Devices Safety Review

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Dear review team,

Please find below my answers to the questions posed at the teleconference.

My potential conflict of interest is that I provided assessments for medicolegal cases for pelvic mesh litigation. The requests for all cases were from plaintiffs' attorneys and I've been compensated for my work at hourly rate independent from the outcome of litigation.

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ANSWERS

Question 1:

Our patient groups have said to us that they feel synthetic mesh is unsuitable for long term insertion.

What are your views on this for the use of polypropylene mesh

- *for stress urinary incontinence?*
- *for pelvic organ prolapse?*

Is there such a thing as medical grade polypropylene? If so what is it?

Answer:

My opinion is that assessment of suitability should be based on a long-term risk/benefit profile of a device compared to non-mesh surgeries and non-surgical approaches. My recommendation for the review team would be to conduct an independent literature review and possibly a patient satisfaction survey. There are several factors that need to be considered in assessment of the long-term risk/benefit profile:

i. Data comparison

A simple approach could be to compare cure (fail) rates and rates of complications for mesh and non-mesh approaches as well as non-surgical treatment. In practice, published numbers are highly heterogeneous due to differences in methodologies of data collection, length of follow up, criteria to define complications and cure rates etc. My recommendation would be to compare methodologically similar studies and select type of studies that can yield better quality data. Some of the main issues are discussed below.

ii. Cure rates

In the literature there can be objective parameters of anatomical correction (measurements of prolapse etc.) and subjective alleviation of symptoms felt by the patients (patient satisfaction). Patient satisfaction is likely a better measure as we need to treat patients, not numbers. My recommendation would be to consider both objective and subjective measures reported in the literature. Studies of patient satisfaction for mesh and non-mesh procedures,

if available, can provide patient-centered information. The review team may also consider conducting an independent survey, subject to practical considerations, availably of patient data, and randomization to avoid bias.

iii. Definition of complications

As for any new treatment approach, complications can become evident only some time after introduction of the approach. There is a period when some symptoms may not be readily attributed to a drug or an implanted device. Therefore, initial studies may not include all complications. Also, less experienced providers may not connect a symptom with a drug or a device. Based on published literature and my experience with medical records of mesh excision cases the complications can be split into groups/symptoms:

i. Vaginal mucosal erosion. This was the first complication described in publications and it is readily diagnosed by even less experienced clinicians.

ii. Pain, including dyspareunia. This may not be readily associated with mesh and may be under-reported. Less experienced clinicians may only attribute pain to exposure, not realizing that similar tissue damage can occur deeper in the tissues. Scarring, mesh contraction, tissue distortion, direct nerve involvement and other mechanisms can contribute to mechanisms of pain without mesh exposure. The review team will likely encounter a significant heterogeneity in the publications as studies vary in the definitions and criteria to associate pain with mesh.

iii. Hispareunia. This term was introduced into literature after reports of male discomfort during intercourse due to exposed mesh.

iv. De novo urinary symptoms (urge incontinence, recurrent UTIs, outflow obstruction etc.) These symptoms can be caused by either compression of the urethra/bladder neck without mesh erosion or it can be caused by mesh erosion into the urethral/bladder wall. The erosion can be partial, without mesh exposure in the lumen of the urethra or bladder. These partial erosions can be underdiagnosed. The symptoms may be also underdiagnosed due to overlaps with the pre-existent urinary symptoms. Complete transmigration through the wall of an organ is more readily diagnosed as mesh is visible in the lumen on cystoscopy. It also has more advanced symptoms such as UTIs, stone formation etc.

v. Rectal symptoms, including rectovaginal fistula. Based on my review of the published literature and records, these can be most devastating complications. As for urinary symptoms they can occur with or without mesh erosion into the rectum and the severity would depend on the degree of penetration. In cases I encountered, complete transmigration into the rectal lumen resulted in recto-vaginal fistula.

vi. Bowel adhesions. This complication is mainly applicable to sacropexy mesh. If exposed into the peritoneal cavity, bare mesh or granulation tissue will trigger adhesions. These may or may not be associated with mesh since any intra-abdominal surgery poses risks for adhesions but the risks are significantly higher with foreign objects.

vii. Infection (clinically apparent). A common scenario for mesh infection is in a setting of mesh exposure. However, I have encountered cases of deep mesh infections without mesh exposure. The infections are more extensive in a setting of mesh transmigration into the bladder or the rectum. More advanced cases present as an abscess or fistula. The infections are usually more extensive in diabetic patients.

viii. Systemic symptoms. These have been recently described in the literature as mesh-related autoimmune diseases or ASIA syndrome. [1] At present, we may not fully understand their mechanisms and association with implants. A complicating factor is that there can be an overlap between concurrent non-implant related autoimmune diseases and mesh-related symptoms resembling autoimmune conditions. From my understanding, further research is needed in this area as we may face a new iatrogenic condition with unique mechanisms.

A coding system introduced by the International Urogynecological Association (IUGA) can give the team another overview of the range of possible complications that need to be searched in the literature. [2]

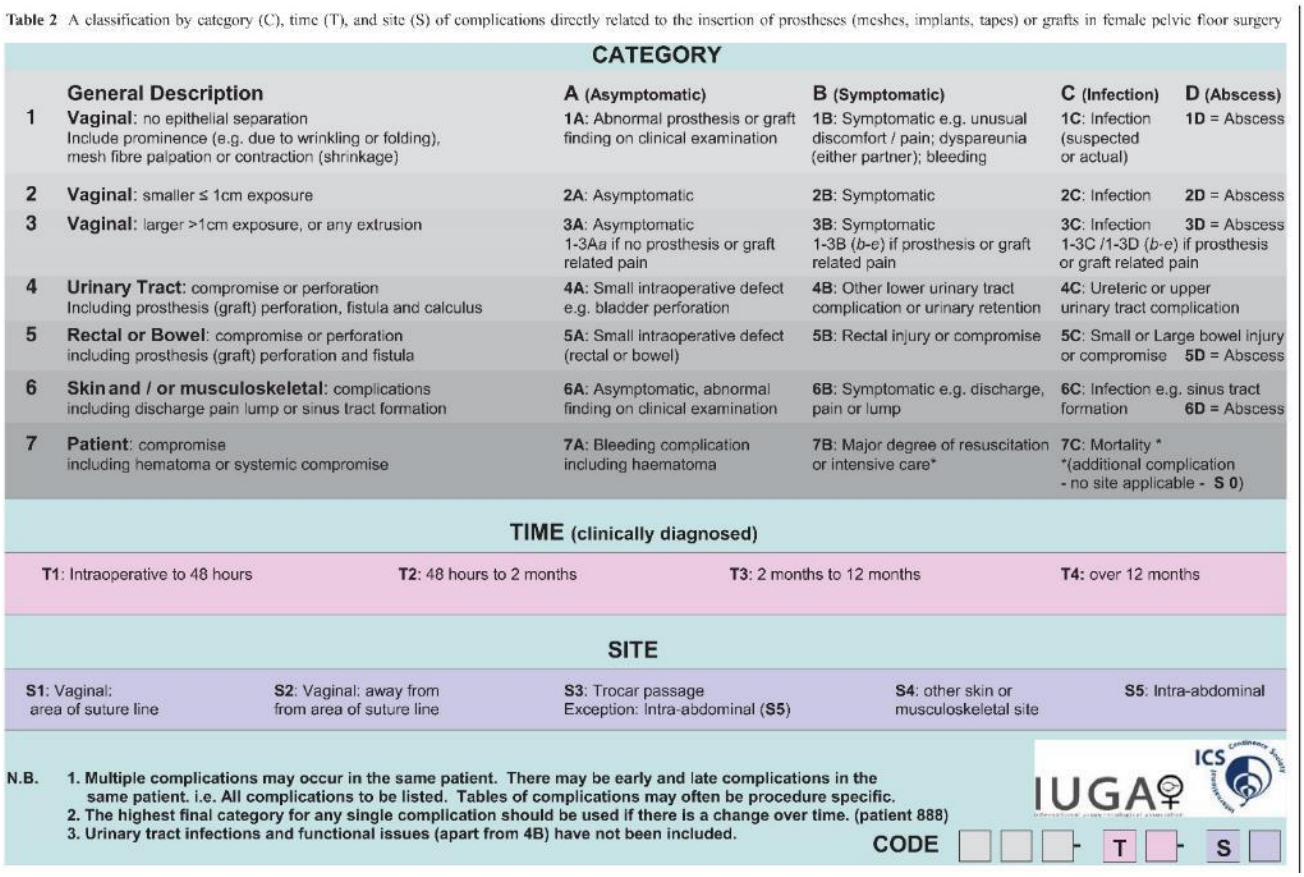


Table 2 A classification by category (C), time (T), and site (S) of complications directly related to the insertion of prostheses (meshes, implants, tapes) or grafts in female pelvic floor surgery

CATEGORY

	General Description	A (Asymptomatic)	B (Symptomatic)	C (Infection)	D (Abscess)
1	**Vaginal**: no epithelial separation Include prominence (e.g. due to wrinkling or folding), mesh fibre palpation or contraction (shrinkage)	**1A**: Abnormal prosthesis or graft finding on clinical examination	**1B**: Symptomatic e.g. unusual discomfort / pain; dyspareunia (either partner); bleeding	**1C**: Infection (suspected or actual)	**1D** = Abscess
2	**Vaginal**: smaller ≤ 1cm exposure	**2A**: Asymptomatic	**2B**: Symptomatic	**2C**: Infection	**2D** = Abscess
3	**Vaginal**: larger >1cm exposure, or any extrusion	**3A**: Asymptomatic 1-3Aa if no prosthesis or graft related pain	**3B**: Symptomatic 1-3B (*b-e*) if prosthesis or graft related pain	**3C**: Infection 1-3C /1-3D (*b-e*) if prosthesis or graft related pain	**3D** = Abscess
4	**Urinary Tract**: compromise or perforation Including prosthesis (graft) perforation, fistula and calculus	**4A**: Small intraoperative defect e.g. bladder perforation	**4B**: Other lower urinary tract complication or urinary retention	**4C**: Ureteric or upper urinary tract complication	
5	**Rectal or Bowel**: compromise or perforation including prosthesis (graft) perforation and fistula	**5A**: Small intraoperative defect (rectal or bowel)	**5B**: Rectal injury or compromise	**5C**: Small or Large bowel injury or compromise	**5D** = Abscess
6	**Skin and / or musculoskeletal**: complications including discharge pain lump or sinus tract formation	**6A**: Asymptomatic, abnormal finding on clinical examination	**6B**: Symptomatic e.g. discharge, pain or lump	**6C**: Infection e.g. sinus tract formation	**6D** = Abscess
7	**Patient**: compromise including hematoma or systemic compromise	**7A**: Bleeding complication including haematoma	**7B**: Major degree of resuscitation or intensive care*	**7C**: Mortality * *(additional complication - no site applicable - **S 0**)	

TIME (clinically diagnosed)

T1: Intraoperative to 48 hours | **T2**: 48 hours to 2 months | **T3**: 2 months to 12 months | **T4**: over 12 months

SITE

S1: Vaginal: area of suture line | **S2**: Vaginal: away from from area of suture line | **S3**: Trocar passage Exception: Intra-abdominal (**S5**) | **S4**: other skin or musculoskeletal site | **S5**: Intra-abdominal

N.B.
1. **Multiple complications may occur in the same patient. There may be early and late complications in the same patient. i.e. All complications to be listed. Tables of complications may often be procedure specific.**
2. **The highest final category for any single complication should be used if there is a change over time. (patient 888)**
3. **Urinary tract infections and functional issues (apart from 4B) have not been included.**

IUGA ICS

CODE ☐☐☐ - T ☐ - S ☐

Figure 1. Coding of pelvic mesh complications. [2]

iv. Sensitivity of studies to detect complications

Studies under consideration should be sensitive to detect complications. Frequently, studies are focused on cure rates of the original condition (stress incontinence, prolapse) but not on the complications. Understandably, complications are not a primary goal of the studies that investigate a new approach aiming to improve outcomes. High rates of complications may have a range of negative effects such as "publishability" in higher ranking journals, funding for further research, time and monetary investments etc. There is also an issue of awareness of the full range of possible complications and their inclusion in the records (discussed in paragraph "iii"). One can only find what he is looking for. Therefore, methodology of the studies may be affected in different ways with resultant underreporting of complications. Generally, there are much less possibilities for over-reporting complications. Overall, long-term (discussed in "v") studies designed to detect the full range of complications have a higher chance to detect true rates of complications.

v. Length of follow up

Timing of complications ranges from days to years and decades after mesh implantation. [3] [4] [5] [6] This means that the rate of complications is not a fixed number but rather a parameter that rises over time to a certain relative plateau. Complications can occur at any time after implantation and a given cohort of patients will continuously accumulate complication cases, although at a gradually slowing rate. In my practice, I have examined specimens of meshes removed anytime between few weeks to 30+ years after implantation. For example, in our experience with hernia meshes excised for complications [7] [8], 50% of excisions (complications) occur within approximately the first 4 years after implantation (Figure 2 below). [9] Then it takes much longer, more than 10 years to accumulate the remaining 50% of complications and reach a relative plateau. This plateau would reflect the long-term complication rates in a prospective study.

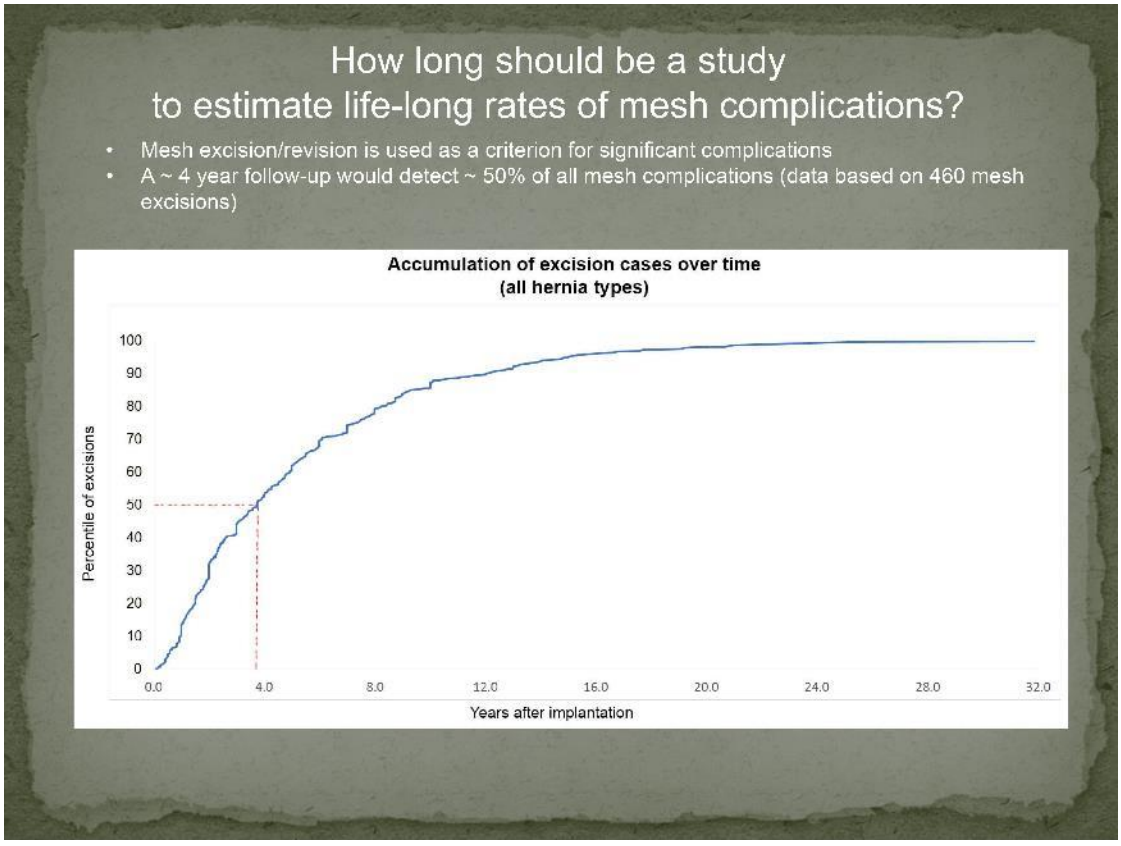


Figure 2. Percentile of excisions vs. time since implantation, hernia mesh excisions. Note that accumulation of complications reached 50%tile at ~4 years after implantation while a relative plateau was reached after 15 years. [9]

Similar data is reported in published literature for pelvic mesh complications. For example, Miklos et al. reported median (50%tile) of 3-4 years between pelvic mesh implantation and excision.

Table 2 Interval between mesh insertion and removal (years)

	Mean (SD)	Median (range)	*p* value
Total ($N = 497$)	3.68 (2.47)	3.0 (0–18)	
Sling ($n = 311$)	3.78 (2.72)	3 (0–18)	0.133*
TVM ($n = 194$)	3.44 (2.00)	3 (0–10)	
SC ($n = 29$)	4.35 (2.42)	4 (1–10)	
Sling type			
RP ($n = 109$)	4.26 (3.22)	4 (0–18)	0.006*
TOT ($n = 134$)	3.69 (2.41)	3 (0–9)	
SIS ($n = 39$)	2.72 (1.64)	3 (0–7)	

*ANOVA

TVM transvaginal synthetic mesh, *SC* sacrocolpopexy, *RP* retropubic sling, *TOT* transobturator sling, *SIS* single-incision sling

Figure 3. Median timing of pelvic mesh excisions is 3-4 years after implantation. [10]

This timing indicates that a prospective study would detect 50% of complications after 3-4 years of follow-up. The rates would be underestimated by 50% at that time. In practice, patients are enrolled during prospective studies and follow up time for most patients is shorter than the length of a study. Therefore, median follow up time, not study length is more important to estimate accuracy of the complication rates. Short studies and studies with short median follow up can provide only partial information of the complication rates. Miklos et al. reported maximum implantation interval of 18 years. For prospective studies, a common problem of long follow up times is rising drop-out rate. The patient become lost to follow up after some time and the causes of drop-outs can introduce biases. Therefore, drop-out proportion and its causes should be considered during literature review.

vi. Causation of complications

I have examined over 500 explanted mesh specimens during my career. In these cases, clinicians determined that an area was either painful, exposed through mucosa, deformed/banded, infected, or mesh eroded through an organ. In over 95% of excisions nature of the lesion was mesh, as a foreign object with tissue reaction to it. Only in a small proportion of cases clinicians made errors in their assessment as for the nature of the lesion and excised other foreign objects such as gauze material, injectable substances, surgical staples etc. I have not yet encountered a case when a non-iatrogenic lesion (natural disease), such as a tumor was mistaken for mesh material or a case where mesh became involved secondarily by such a lesion. Based on this information, it is expected that in cases of mesh excisions clinical assessments of mesh as a cause of complications are fairly accurate. There can be some uncertainty in cases when clinical investigations do not result in mesh excision. In these cases a clinician may either have an uncertainty whether mesh is the cause of a complication (usually pain) or may not perform an excision for technical reasons. Based on my review of clinical records only highly specialized surgeons perform extensive mesh excisions. Less experienced physicians may not know the full range of mesh complications and associate mesh complications only with mucosal erosions, not realizing that tissue damage also occurs internally. Some patients also present with multiple conditions where differential diagnosis can be difficult. Considering these factors, studies that are based on mesh excisions are likely to be of higher value in terms of causation but will underestimate complication rates since not all meshes are excised to treat complications. Without mesh excision, institutions and clinicians with good experience of treating the full range of complications will provide better data in comparison with those who mainly focus on implantations or have limited volumes.

vii. Type of device

Although made of the same type of mesh, monofilament polypropylene, the devices for stress urinary incontinence (tapes) and pelvic organ prolapse are placed in somewhat different locations and affect different areas in the pelvis. At microscopic level tissue reactions to mesh are the same, independent of a device type. However, at a larger scale, complication profiles are different, depending on the affected organs such as the bladder, rectum, bowel, vagina. Also, complications can differ depending on affected anatomical structures such as nerves, vessels, and muscles. Therefore, risk/benefit profiles should be assessed for groups of similar devices:

a) Retropubic stress urinary incontinence slings (tapes)
b) Transobturator stress urinary incontinence slings (tapes)
c) Transvaginal pelvic organ prolapse kits (mesh implant)
d) Sacrocolpopexy mesh for transabdominal placement (mesh implant)

The transvaginal (kit) devices for treatment of pelvic organ prolapse (c) peaked in use around 2012. After that they have been gradually removed from the market or banned for sale. The alternatives were non-mesh surgeries and surgery using mesh - transabdominal sacrocolpopexy (d). This change likely shifted numbers towards sacropexy and non-mesh surgeries in the later years. However, it is likely too early to be reflected in the studies with long-term follow up. This timeline should be also considered during literature review.

Question 2:

We are interested in understanding the physical properties of mesh once it has been inserted, including:

- *shrinkage,*
- *degradation,*
- *leeching of chemicals, and*

breakdown cause by body heat

Answer:

As a pathologist I observe mesh-body interactions at microscopic level. As stated earlier, the devices under question are composed of the same type of mesh – macroporous monofilament polypropylene mesh. At microscopic level tissue reactions are the same for these devices. They are also the same for monofilament mesh used for hernia repair:

i. Inflammatory reaction

Inflammatory reaction to an implant is a non-specific reaction to a foreign body. The main cellular component of a foreign body type inflammation is macrophages. They are recruited in an attempt to destroy the foreign object. They secrete an array of substances such as bioactive lipids, hydrolytic enzymes, reactive oxygen metabolites, and mediators of fibroblast proliferation. [11] [12] The inflammation persists for as long as a foreign object remains in the body. [13] Generally, the degree of inflammation tends to lessen over time, but this is variable between individuals. In some patients the inflammation can be as intense many years after implantation as in some patients few months after implantation. The inflammation damages surrounding tissues and, after the scar is matured, contributes to continuous remodelling of the scar around mesh fibers. [14] The main significance of inflammation is that it damages tissues non-specifically and provides stimulus for scarring.

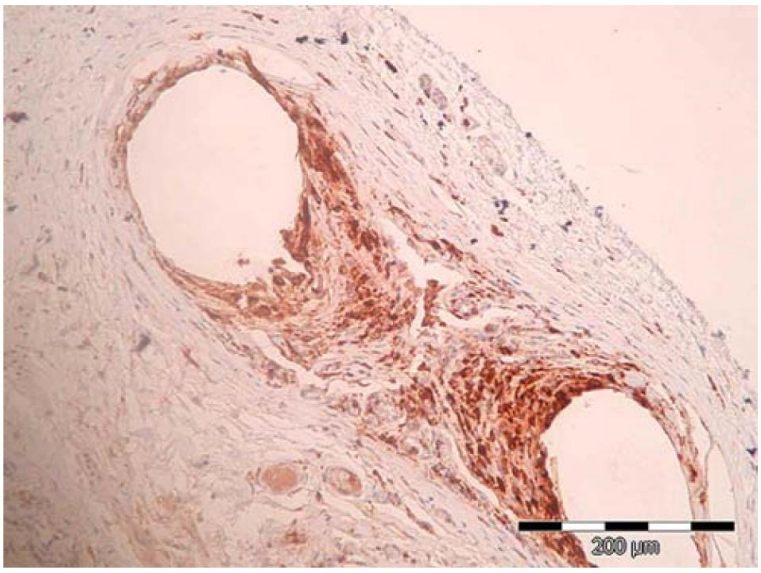


Figure 4. Staining for macrophages (brown) shows foreign body type inflammation around mesh fibers (clear oval spaces). [15]

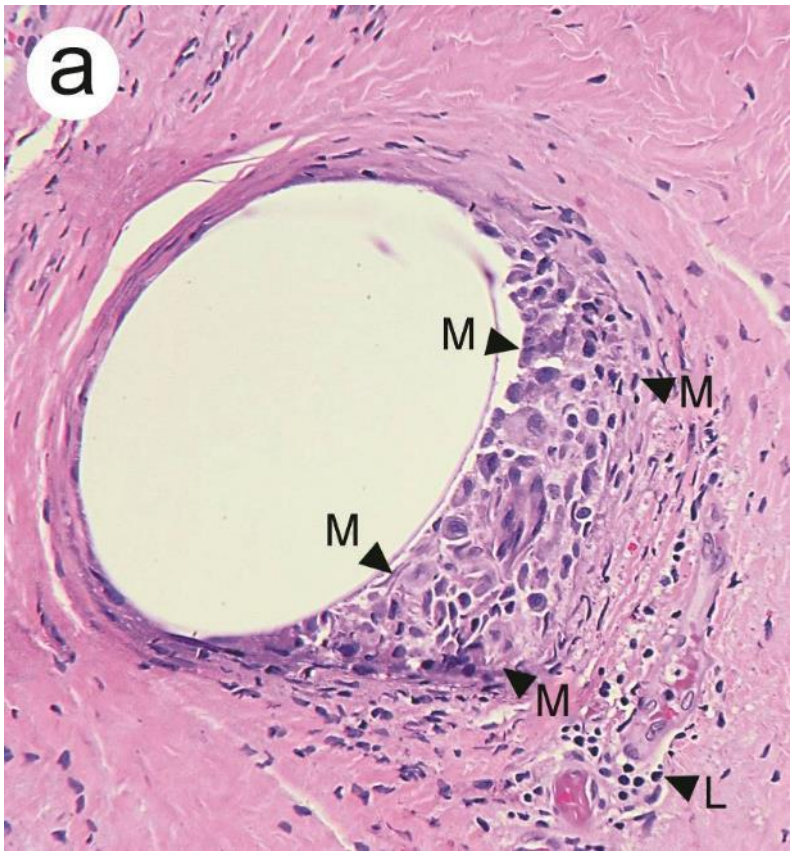


Figure 5. Foreign body type inflammation against mesh is mainly composed of macrophages (between M arrowheads)**.** [16]

ii. Mesh integration and scarring

Mesh integration into the tissue is a result of repair mechanisms. As in any wound repair, these mechanisms aim to restore continuity of the tissues. Mammalian connective tissues do not regenerate except at foetal stages. [17] [18] [19] [20] Instead, the damaged tissues and void spaces are filled with a non-specific reparative tissue - scar**.** This reparative type of fibrous tissue is used by our body as a universal glue or filler. The reparative tissue is non-specific as it is used to repair a variety of damages: mechanical cuts, burns, infectious and non-infectious inflammatory damage. Reparative tissue in wounds is usually called "scar", while similar tissue laid within organs after an inflammatory damage is usually called "fibrosis" (lung fibrosis, liver cirrhosis etc.).

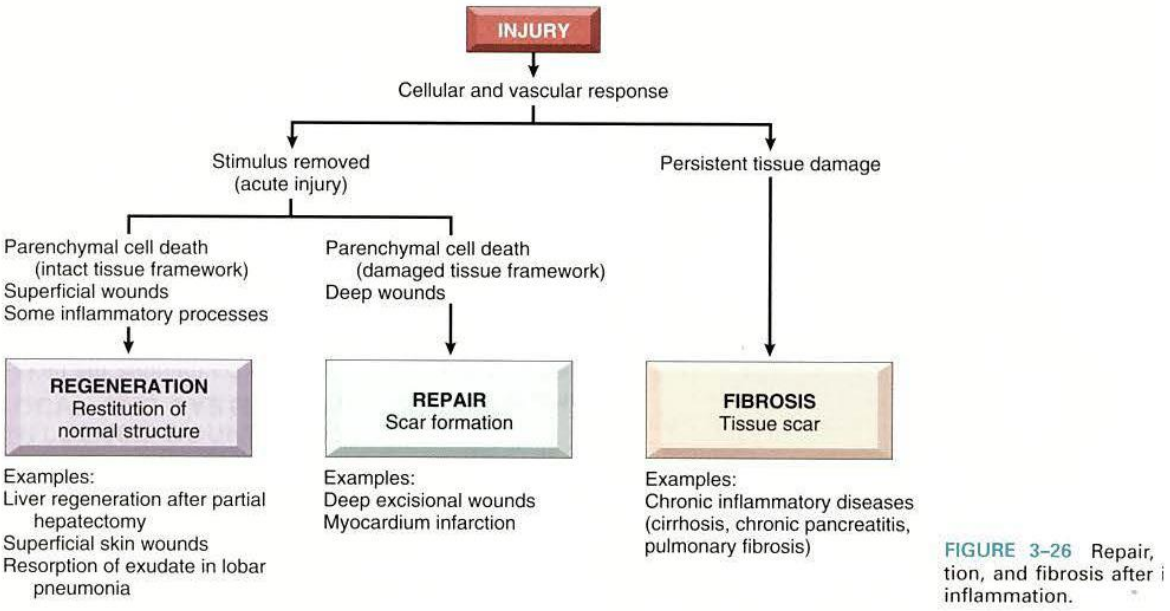


Figure 6. Diagram showing the pathways of regeneration and repair. P. 107-108 [20]

In relation to a foreign object, the body needs to repair damaged tissue as well as to deal with the foreign object as it is recognized as potentially harmful. Although variable in intensity, these processes are the same for all foreign objects: implants and traumatic foreign objects such as pieces of glass, metals, wood etc. There are two zones of reaction around a foreign body: inner zone of inflammation immediately at the foreign body surface and an outer zone of scarring forming a scar capsule:

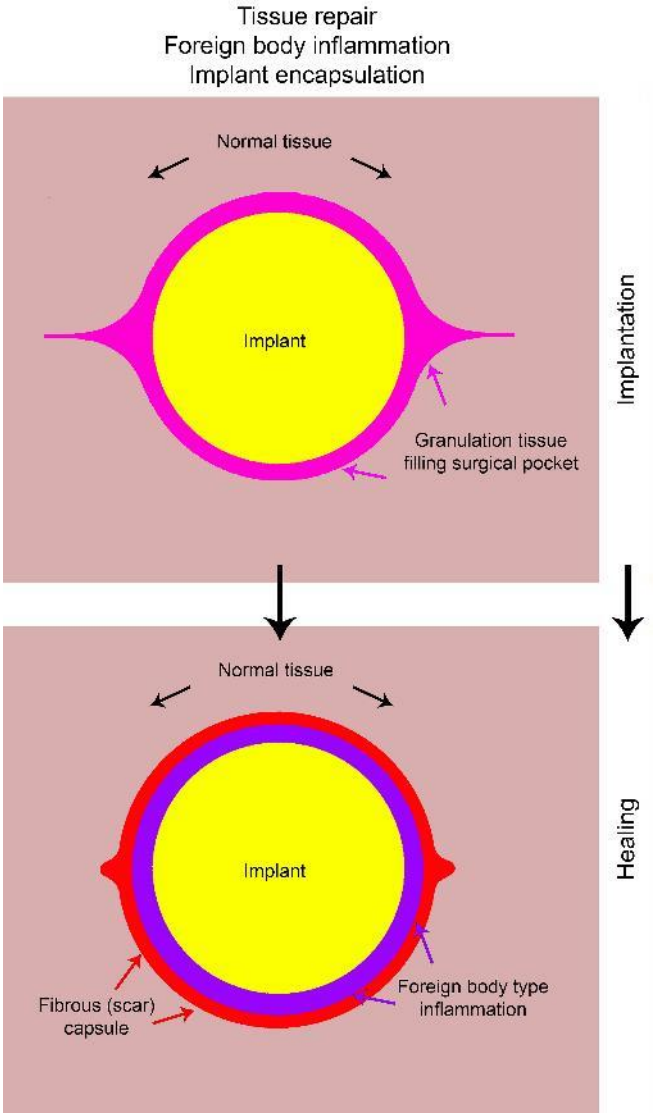


Figure 7. Drawing showing two zones of tissue reaction around a foreign object – inflammation and scar encapsulation. [21]

After surgery, the void spaces around and within mesh are filled with clotted fluids. While macrophages clean the area, fibroblasts migrate from the viable edges. [20] [19] This initiates propagation of granulation tissue into the mesh spaces from the viable tissues surrounding mesh. The initial loose collagenous matrix with abundant capillaries forms granulation tissue. In cases of implanted mesh granulation tissue surrounds the mesh and propagates into the spaces within the mesh structure, such as folds, curls, pores and interstices between mesh fibers, provided they are large enough for tissue ingrowth. [22] Over a course of weeks, the amount of deposited collagen grows, while fibroblasts, previously producing collagen acquire contractile filaments and transform into myofibroblasts. Myofibroblasts' function is somewhat similar to muscle fibers. They can contract and shrink the area of scarring. Their contractile function together with reduction of extracellular fluid and collagen cross-linking result in wound contraction. The process is aimed to minimise the volume of maturing scar. For scar tissue within and around mesh, the contracting forces act within and around mesh and pull mesh fibers together. As a result, the entire mesh becomes contracted. [23] [24] [25] [26] [27] During this stage collagen becomes more organized, and the density of microvasculature recedes. The scar tissue becomes more compact. The repaired area becomes dense hypocellular scar, which then is slowly remodelled further depending on tissue forces, repetitive damage, damage form inflammation etc. [28] [29] [30]

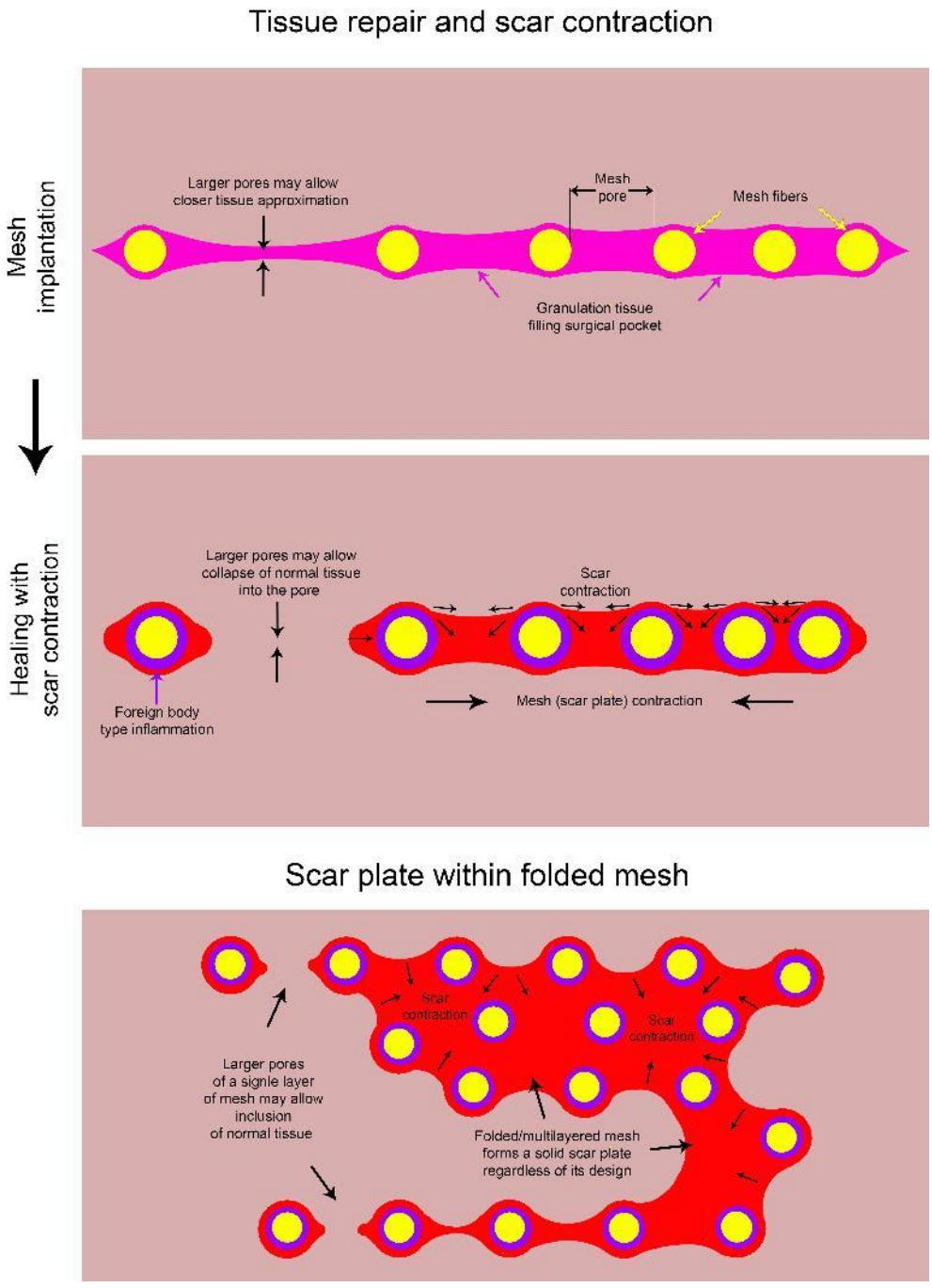


Figure 8. Healing within and around monofilament mesh, cross-sectioned mesh fibers are filled yellow. Scar tissue (red) fills pores and folds within mesh. As scar tissue contracts during maturation it pulls mesh fibers closer to each other and the entire device contracts [21]

Some larger pores may include fat or other components of normal connective tissue that passively collapses into the pores. Mesh designs containing pores of several millimetres (lightweight) have a greater chance to contain normal connective tissue in the larger pores of their complex structures. [31] [32] In pores where scar fills pores or bridges from fiber to fiber across the pores, it is termed “bridging fibrosis”. Scar tissue inside mesh together with the scar encapsulating the entire mesh form a composite mesh-scar plate or a “scar plate”. Scar tissue also provides connections between the composite mesh-scar plate and the surrounding normal tissues. [28]

The scarring, along with other mesh-related tissue changes, is an important factor in the mechanism of complications. That is why an entire direction of research and development in the field of implantable meshes was dedicated to minimizing scarring and its negative effects. [31] [33] [34] This research led to the development of lighter-weight larger-pore mesh designs. However, the design only shows benefit if the mesh stays flat in a single layer. The pores should also stay large after mesh deformations such as stretching and contraction. The benefit of larger pores becomes irrelevant in folded, multilayered mesh and in the designs that allow significant pore collapse. For example, it is more problematic to keep mesh flat in the groin or in the pelvis, since the locations are not flat and subject to movement and bending. The mesh can fold and bunch, and the scar fills the spaces between the folds. The phenomenon was termed “meshoma” since the mesh forms a tumour-like mass (-oma). [35] [36]

Scar tissue affects flexibility and elasticity of implanted mesh. Elasticity and flexibility of knitted meshes is dependent on bending and movement of the mesh fibers. The degree of movement freedom becomes significantly restricted by the ingrown collagenous scar. At the same time, the embedded mesh acts as a rebar reinforcement for the scar tissue limiting its native flexibility and elasticity. The resultant mesh-scar composite structure is stiffer than the original new mesh or scar tissue without mesh. The resultant stiffness is dependent on mesh design with its own physical characteristics as well as the amount of induced scarring. [37] [38] [23] [33] [39]

A stiff implant affects surrounding tissues. It has been shown that native tissues surrounding an implant undergo weakening. Published data indicated a non-age related loss of strength of the surrounding tissues after mesh implantation. [40] [41] This occurs

due to physical loads being transferred to the implant, while native tissue undergo partial atrophy in a "braced" position. [40] There is also the age-related loss of strength that needs to be considered as mesh implants are permanent. The overall effect is that the mesh stiffens over time while the tissues become weaker through a variety of mechanisms. This leads to a growing mismatch between the implant and the tissues.

iii. Tissue innervation

After any injury axons of interrupted nerves grow to re-innervate their targets. [42] [43] This process can lead to painful scars. [44] [45] [46] [47] [48] The process of scar innervation also takes place in the scar tissue within and around mesh. It has been shown that the nerves can grow into mesh pores, provided the pores are large enough. [49] Higher degree of innervation within mesh has shown an association with the risk of pain as a long-term complication. [7] Normal nerves would conduct sensations from the areas around mesh, including mechanical effects of the mesh and scarring on the tissues. Some nerves can also be affected directly by the mesh fibers. Traumatized nerves can form traumatic neuroma type lesions. Traumatic neuromas are formed when a nerve is damaged and attempts to regrow within scar tissue. [50] [51] They are typically painful lesions. For example, traumatic neuromata commonly occur in amputated limbs. This leads to pain sensation felt in an area that does not exist anymore. The nerves can also form similar lesions in the mesh, either in their attempt to grow through the mesh or disrupted by migrating mesh fibers. [7] [31]

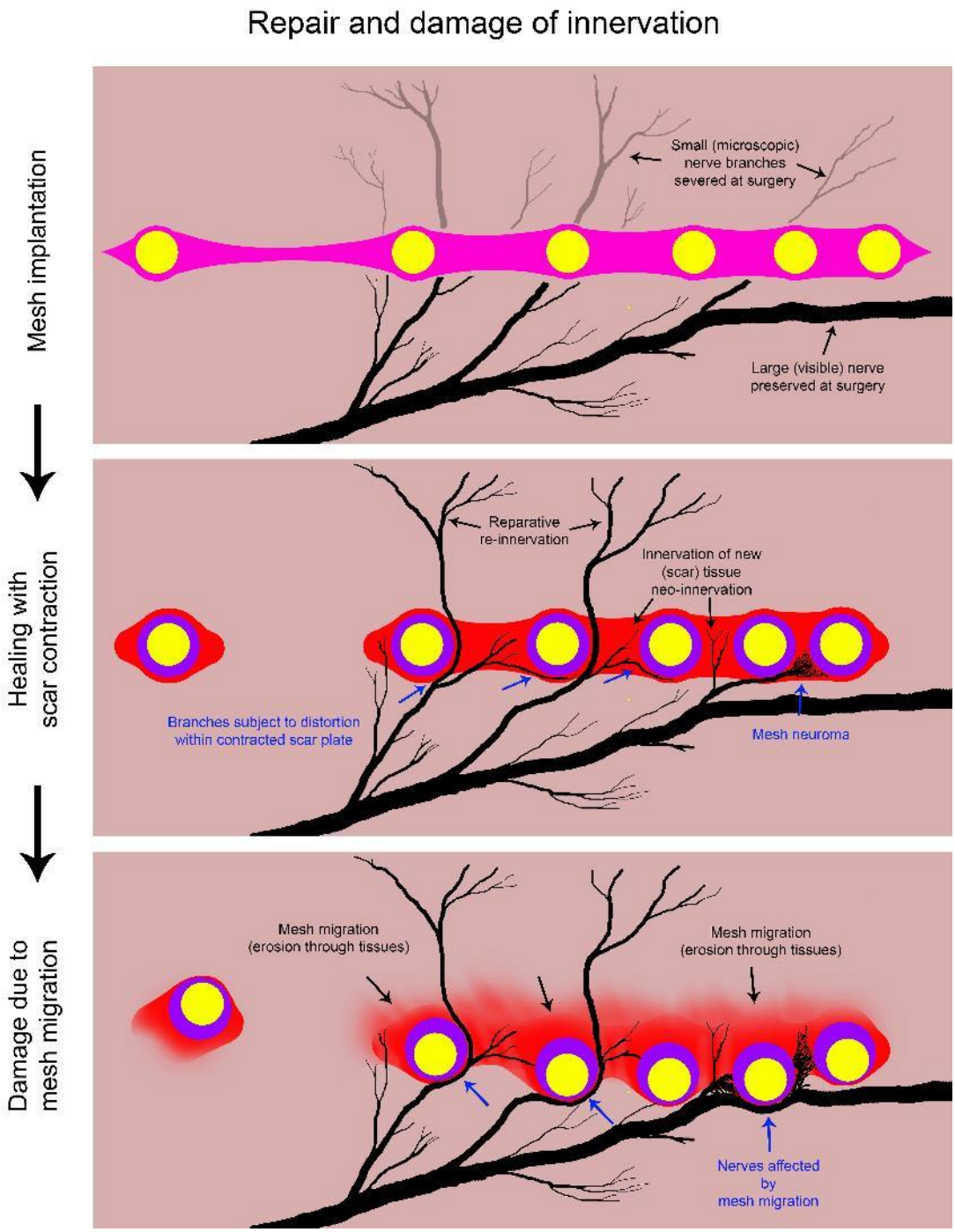


Figure 9. Diagram showing restoration of innervation after surgery and mechanisms the nerves can be affected directly by the mesh. [21]

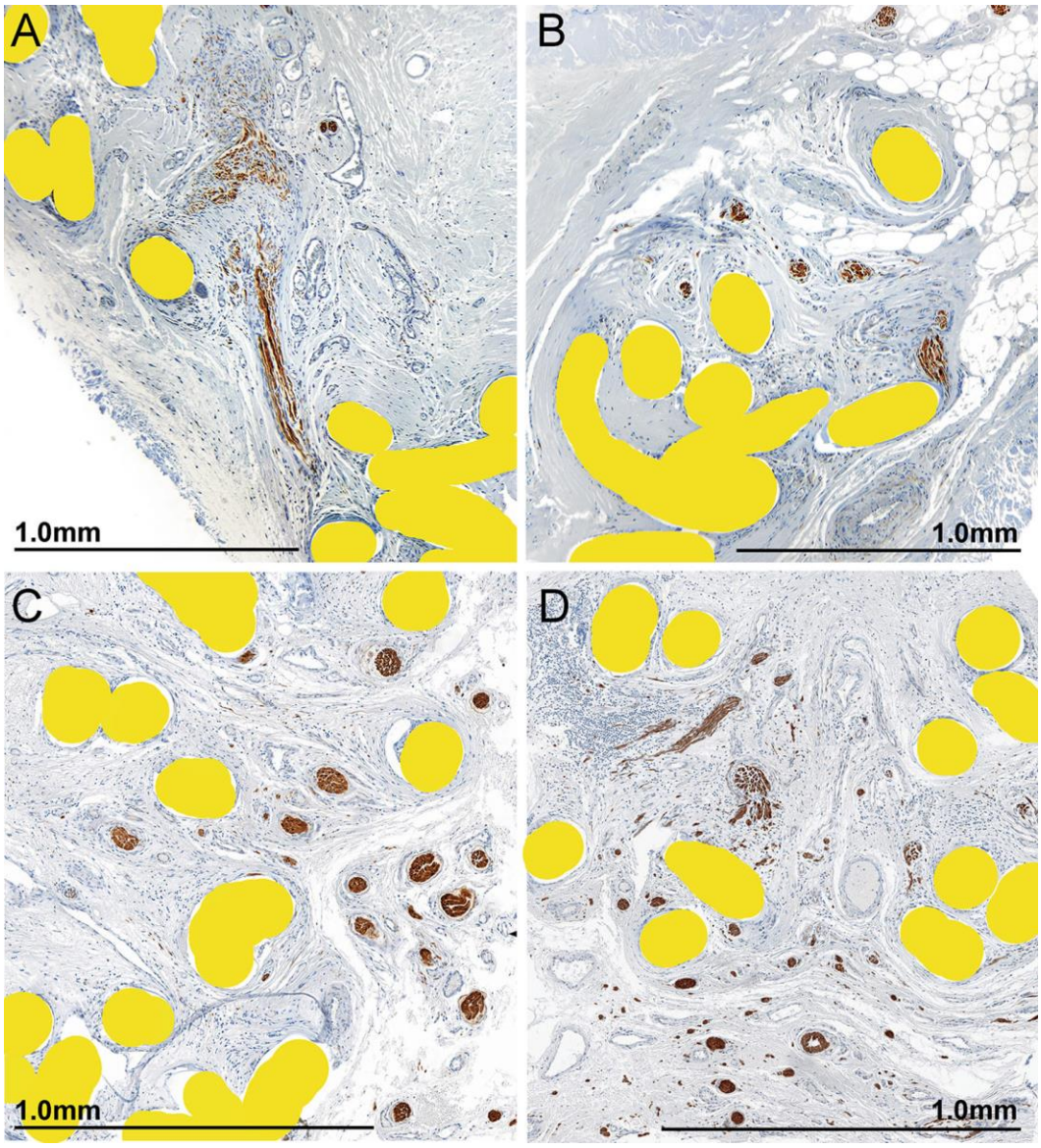


Figure 10. Growth of nerve branches into mesh (A-D) and neuroma formation (A), nerves are stained brown, cross-sections of mesh fibers are filled yellow. [7]

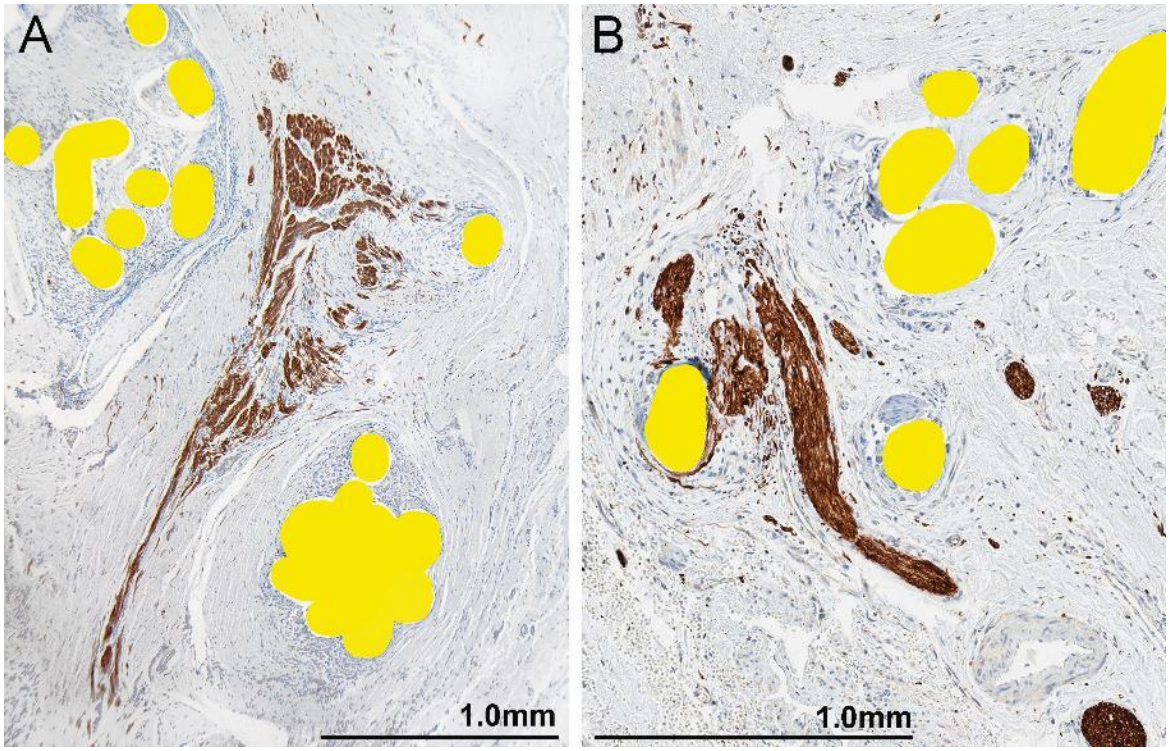


Figure 11. Neuroma formed within mesh structure due to a nerve damaged by mesh fibers (A), tight position of a nerve between mesh fibers (B). [7]

iv. Mesh migration/erosion through tissues

Two types of migration were outlined: primary migration of unsecured mesh within surgical pocket, and secondary migration through tissues. The latter occurs either during or after mesh integration into tissue. Ability of foreign bodies to migrate through tissues and organs is established knowledge. [52] [53] [54] [55] [56] [57] [58] It is a slow internal erosion of the mesh through the tissues. [59] [54] When the tissues cannot withstand the forces, mesh fibers gradually disrupt tissue components and erode through them. This slow migration can lead to disruption of important anatomical structures such as nerves, neural ganglia, vessels and walls of organs. These effects are seen in both, hernia and vaginal mesh devices. [60] [61] [62] [63] [64] [65] [66] [67] [59] [54] Variety of forces, such as intrabdominal pressure, mesh contraction, organ movements, and muscle contraction act to displace the mesh. At the same time, foreign body inflammatory reaction and general ability of tissues to remodel or become disrupted under chronic pressure provide the path for migration. There is likely movement of mesh in every patient, but the distance and extent are variable between the patients. In some patients the movement is clinically insignificant. However, in some patients mesh transmigrates through the full thickness of organ walls such as the bladder or bowel. Symptoms of mesh migration/erosion will depend on the structures damaged on the path of migration. Erosion of mesh through mucosal surfaces or skin exposes the tissues and the mesh to bacterial contamination. This can lead to subclinical or clinically apparent infection. Depending on timing and sequence of events, in some cases mesh becomes exposed through a non-healing operative incision, rather than through a healed surface or other sites. A never healed operative wound is complicated by the presence of a foreign object in the wound. Although can be partially dependent on surgical technique, mesh is a factor in these early erosions. Presence of a foreign body is a known factor for interrupted healing. [20] In relation to erosion through healed skin or mucosa, published literature indicated that mesh specific factors play a role. [68] [28] Variable materials showed different risks for mesh exposure. [69] [70] [71] [72] [68] Animal models showed that the rate of erosion was also dependent on mesh size, where larger mesh implants had a higher risk of exposure. [24] [73] Overall, the published literature and cumulative clinical

experience demonstrated that the risks of mucosal exposure are, among all other factors dependent on device design. [28] [74] [75] [76] [77]

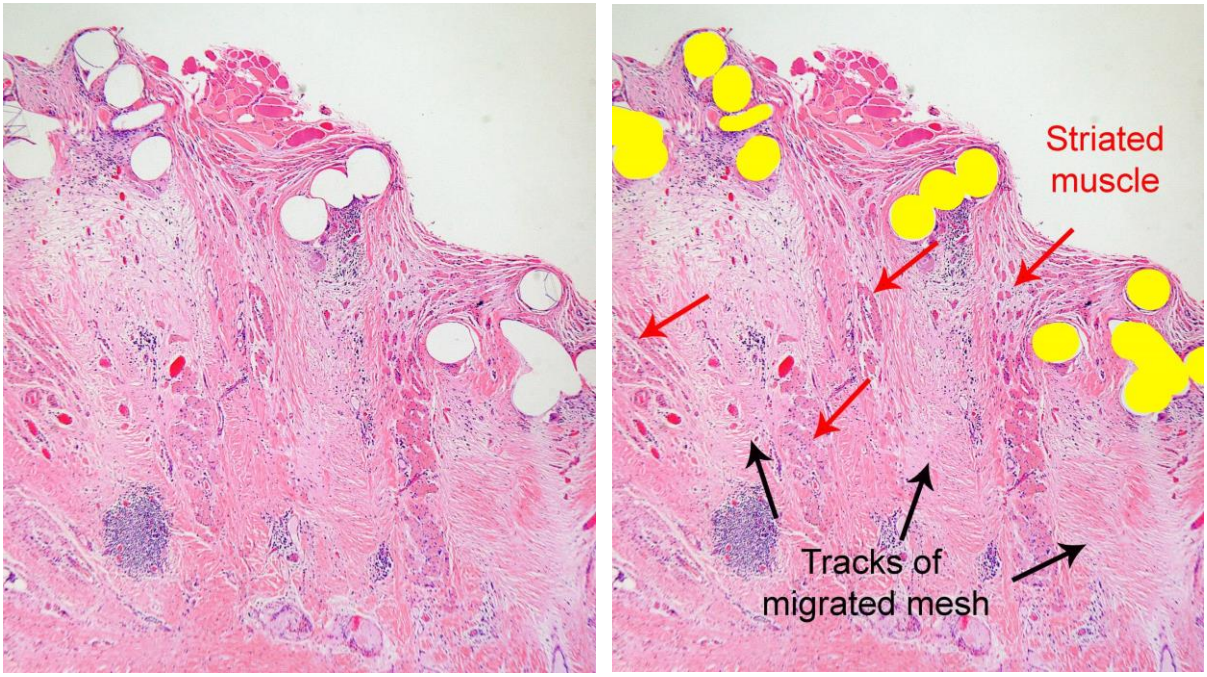


Figure 12. Migration/erosion of mesh fibers through striated muscle. [66]

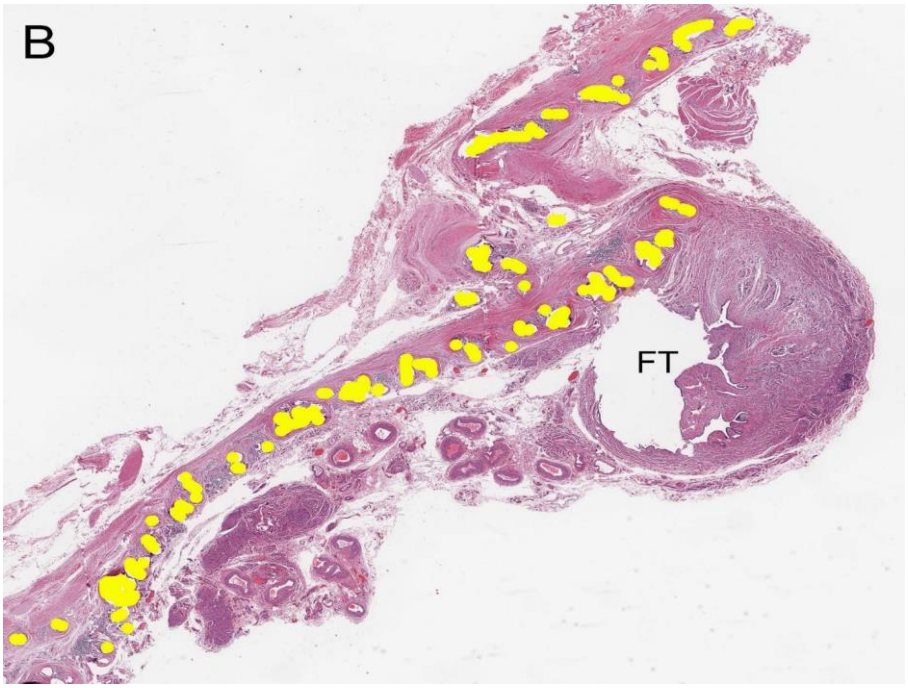


Figure 13. Hernia mesh migration into the fallopian tube (FT). [8]

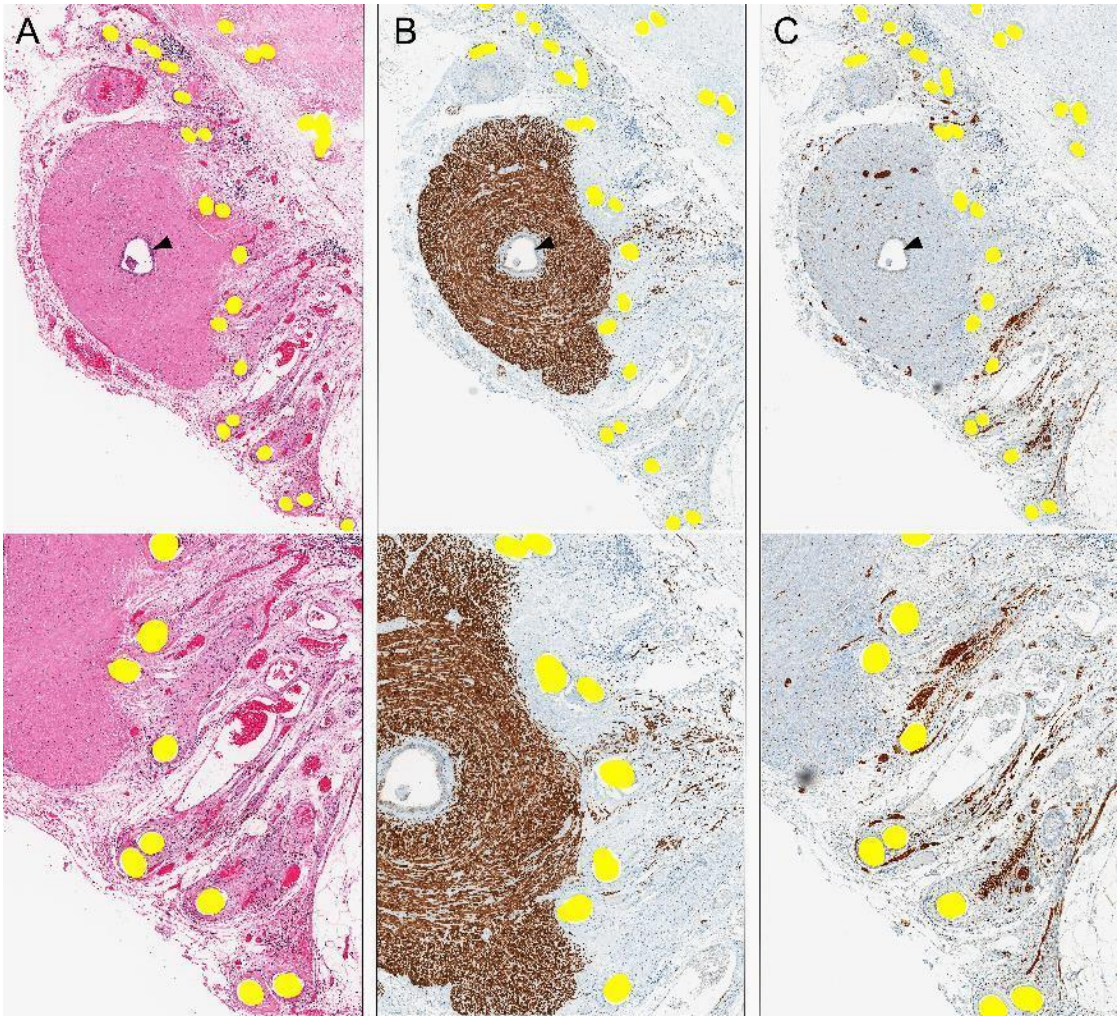


Figure 14. Hernia mesh migration through spermatic cord structures. [8]
Slides of the same block are stained by 3 stains: H&E (A), desmin (B), and S100 (C); mesh fibers filled yellow, vas lumen indicated by arrowheads, 40x magnification in the upper half of each panel (A, B, C), and enlargements to 100x in the lower half. A, Mesh fibers clearly eroded into the vas; hence, it could not be separated from the mesh intraoperatively. Note the trail of scarring, inflammation, and stretched blood capillaries left behind the migrating mesh fibers. B, Desmin stain to show the muscular layer of the vas (dark brown). The muscle is being replaced by scar tissue as the mesh moves through the vas. Note sparse residual muscle fibers on the right behind the advancing mesh (migrating to the left). C, S100 stain to highlight the nerves (dark brown) that are stretched and disrupted by the migrating mesh fibers.

v. Mesh folding/curling

Any soft material can fold. Earlier, during the search for "ideal mesh", knitted meshes were found to be more prone to fold and curl edges. [78] Mesh folding is routinely observed in explanted mesh devices. [30] [49] Similarly to migration, folding of a flat mesh can be primary due to intra-/perioperative movement of unsecured mesh, or secondary, slowly occurring after tissue ingrowth. Immediate postoperative folding can be caused by muscle contraction and organ movement adjacent to the mesh. The mesh may be placed flat during surgery when the muscles are relaxed and the body is in a supine position. After surgery, muscles start contracting, organs shift with body movements, and the bladder and bowel change shape during their function. While human tissues can contract and expand and organs can move back to their previous position, there is no force in a folded mesh to stretch it back. Once folded, it stays folded. Mesh folding/wadding is also further aggravated by scar contraction. [23] The literature demonstrates that the softer lighter weight designs are more prone to folding than the stiffer heavier weight meshes. [39] This property reduces advantages of the lighter weight mesh and the overall result can be worse than for a stiffer mesh that remains flat. Wadding of the mesh into a bulky clump has been termed "meshoma" by hernia surgeons and it is a recognized complication frequently requiring mesh excision. [35] [36] Mesh folding became a serious problem in larger transvaginal (kit) devices. [79] [80] [81] These devices have been withdrawn from use and reclassified as high-risk. [82] [83] [84] For stress incontinence slings, edges of the tapes can curl towards the mucosa increasing risks for exposure. In extreme cases this curling can result in a complete roll (roping). This is likely caused by stretching of the slings where the mesh cannot spring back as it is held by the ingrown tissue. A narrowed roped sling is more likely to cut into the urethra.

TABLE II. Presence of Folding, Calcification, and Bridging Observed at Explanted Mesh Materials, and Partial Volume of IF and of CT at the Interface to the Mesh Material in Dependency of Mesh Class (Large Pore = Class 1, Small Pore = Class 2)[6]

	Large Pore Class 1	Small Pore Class 2	*p*
Folding	59% (n = 101)	47% (n = 211)	<0.05
Calcification	8% (n = 13)	23% (n = 104)	<0.05
Bridging	21+/−9%	85+/−21%	<0.05
IF	18+/−11%	34+/−11%	<0.05
CT	21+/−9%	31+/−9%	<0.05

IF, partial volume of IF; CT, partial volume of CT.

Figure 15. Lighter weight meshes have been reported to be more prone to folding. [39]

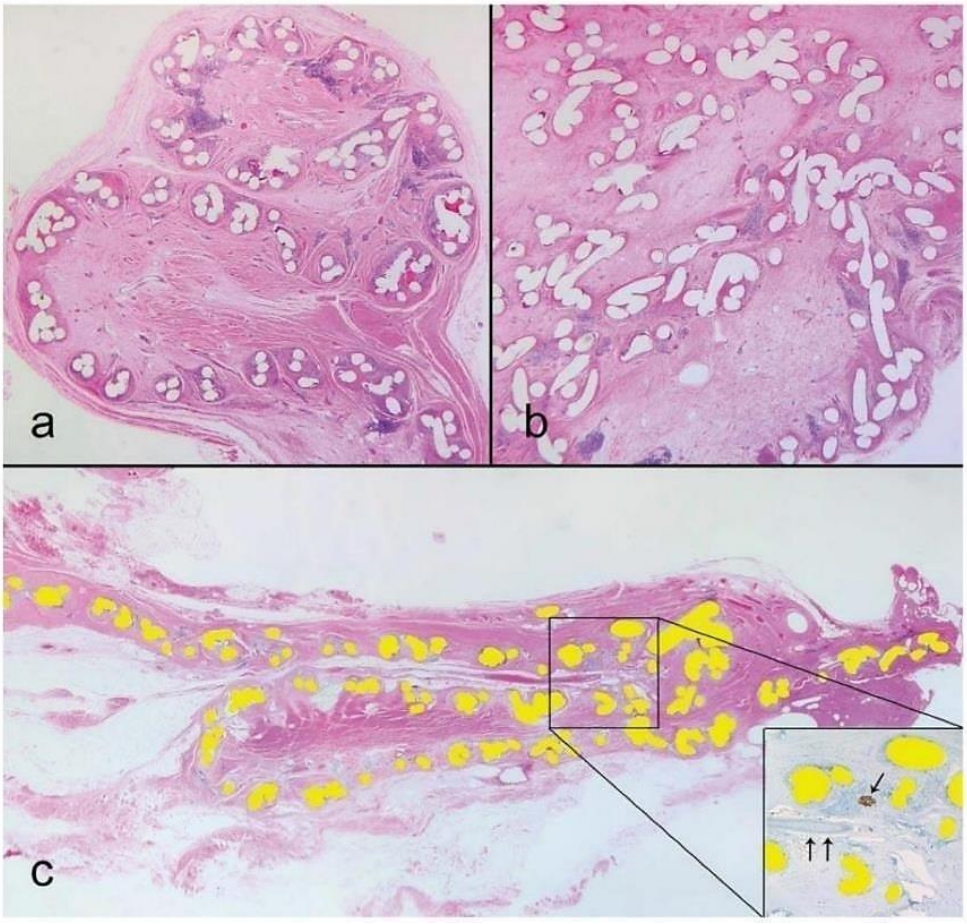


Figure 16. Folding of mesh as seen in histological sections. [49]

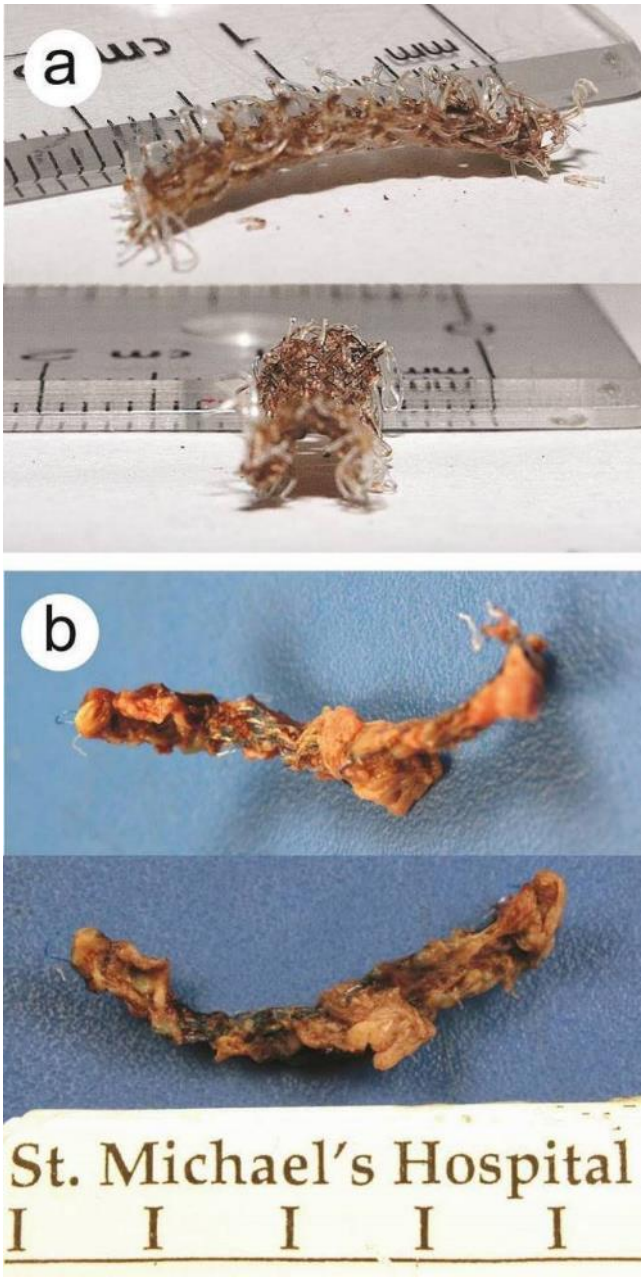


Figure 17. Edges of stress urinary incontinence slings (tapes) can curl. If a curl occurs in the body it can become fixed by the ingrown scar. [16]

vi. Effect on blood vessels

Having examined over 500 mesh explants my observation is that larger vessels do not penetrate mesh. There are capillaries and smaller blood vessels within the tissue inside mesh pores and folds, however larger supplying vessels are present only at the mesh interface. This indicates that blood supply to the tissues on the distal (downstream) side of mesh needs to circumvent mesh. This can be problematic for larger devices, especially folded and located more superficially. Thinner mucosal flaps generally have less vascular reserves and the situation is aggravated by the underlying bulky object of folded mesh. It was likely one of the factors for higher erosion rates of the transvaginal (kit) devices for pelvic organ prolapse. This factor is also important in sacropexy meshes as they are larger devices. Sites that become surrounded by mesh, for example apex of the vaginal vault may have limited access for larger supplying vessels. The apex is one of the common areas for mesh erosion. One of the other contributing factors is concurrent hysterectomy which places more demands on healing in an area with a potential vascular compromise.

vii. Infection

Clinically detectable infection (different from subclinical/dormant) occurs only in a proportion of mesh implants. As for any foreign object, infection can be either introduced with the mesh during implantation, or mesh can become seeded later, through mucosal exposure or hematogeneously, through blood stream from a distant site. In either scenario, surface and spaces within the mesh structure provide adhesion and shelter opportunities for bacteria. Materials with smaller spaces in the mesh structure are more prone to retain infection. [85] The key feature is to allow free traffic of the immune cells - neutrophils. These cells are recruited to fight bacterial infections. [20] Microporous and multifilament meshes contain spaces with limited access for the immune cells, therefore introduce higher risks for infection. [85] [86] [87] [88] Macroporous and monofilament mesh designs can also become infected, although these tend to have more limited spread of infection. In cases of mesh erosion through the bowel infection can be destructive and extensive with subsequent risks of abscess, fistula formation and sepsis. Diabetic patients also tend to have more extensive spread of infection along the mesh and deeper tissues.

Question 3:

What are your views on whether mesh degrades in vivo, and if so, how does it do so and what causes this?

Answer:

Earlier studies showing that polypropylene changes in vivo date back to the 1970's. [89] It was determined at that time that non-stabilized polypropylene degrades in the body. Antioxidants need to be added into resin to retard degradation. It is my understanding that all polypropylene mesh products on the market contain antioxidants and other technical additives. However, it was never shown that the antioxidants remain effective indefinitely throughout the entire thickness of the fiber. Subsequent studies indicated that polypropylene on the market degrades while in the body. [89] [90] [91] [92] [93] [94] [95] Most conclusions were based on observation of surface cracking of explanted mesh filaments using scanning electron microscopy.

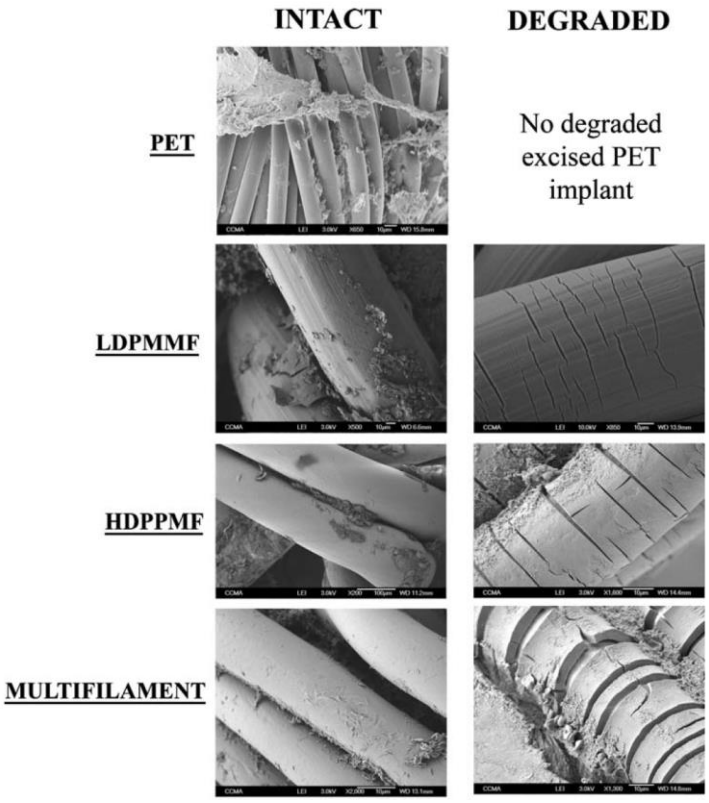


Figure 18. Scanning electron microscopy images of the degraded surface**.** [93]

Later, approximately at the time when mesh drew more attention due to looming litigation, these findings were questioned suggesting that there could be interpretive errors of the scanning electron microscopy observations. [96] [97] [98] However, polypropylene degradation in other environments, such as high temperature, sunlight, and bacterial exposure show changes similar to that of polypropylene exposed to the body environment. [99] [100] [101] It was also found that the cracking layer does not form on other implanted polymers. For example, it has been shown comparing polypropylene and PVDF implanted at the same time. [102] My contribution was to describe polypropylene degradation in cross-sections, using histological sections and transmission electron microscopy. [30] [29] [103] [104] An external zone of altered polypropylene slowly propagates from the surface and becomes visible several months after implantation. The degraded layer forms a continuous tree-bark like shell at the entire surface of mesh fibers. Although relatively thin in relation to the fiber diameter, it forms a tube-like sheath. As any tube type structure, it has a high mechanical efficiency relatively to its thickness.

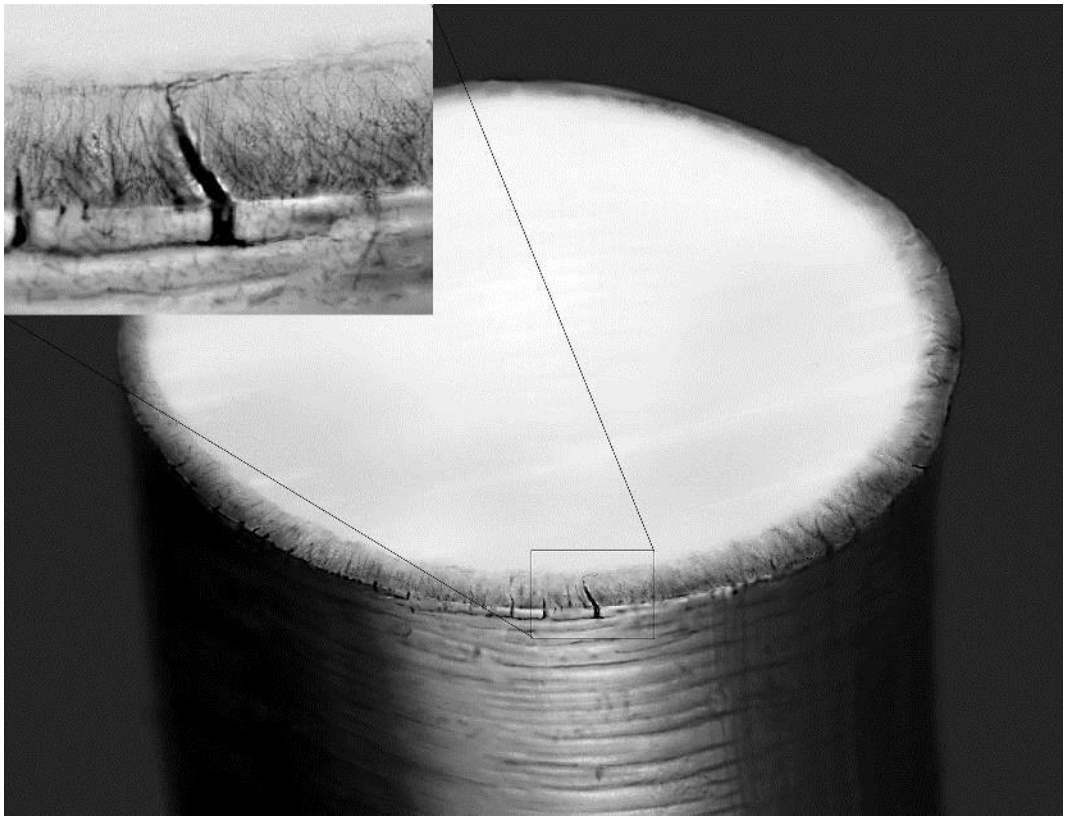


Figure 19. A 3-D restoration of a cross-sectioned mesh fiber. [104]

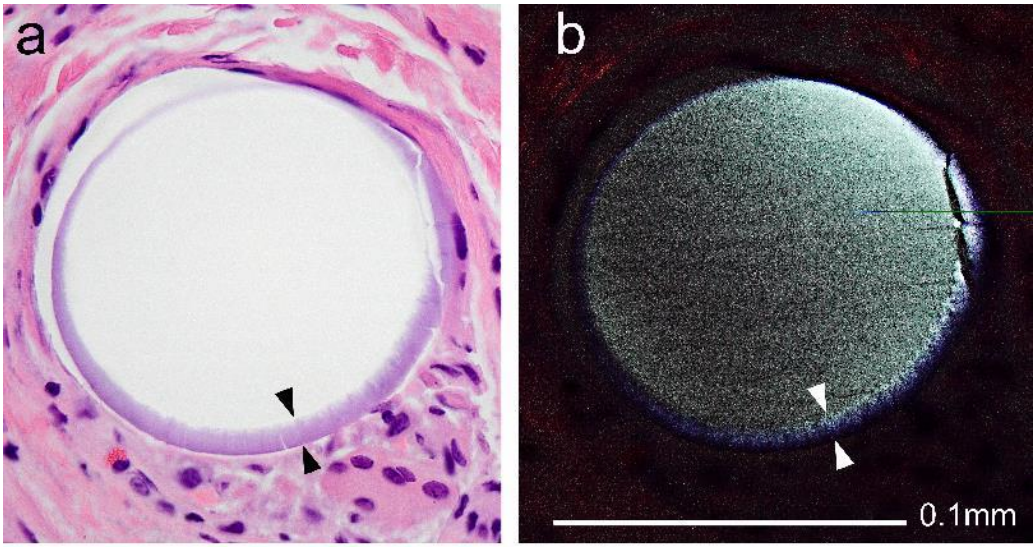


Figure 20. Appearance of degradation "bark" in regular and polarized light. A mesh fiber of a monofilament polypropylene mesh is cross-sectioned and stained by regular histological dyes. Note that a circumferential layer at fiber surface retained the dyes and appears purple (a, between arrowheads). The non-degraded core material appears clear as it does not retain dyes. The degraded layer has optical properties of polypropylene and is bright in polarized light as is the core (b). [104]

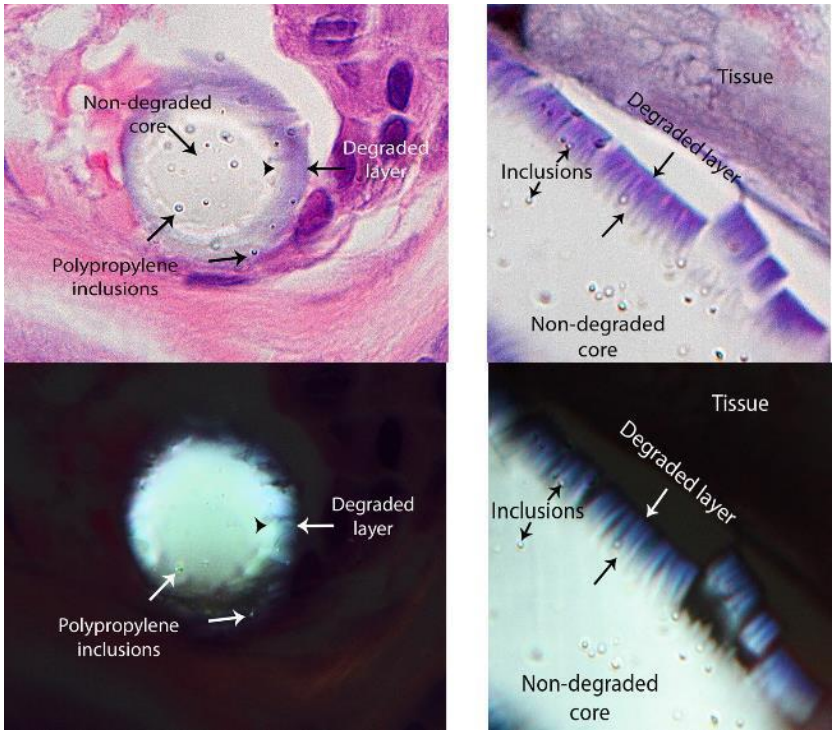


Figure 21. Similar findings in a multifilament polypropylene mesh. [87]

Noteworthy, thickness of the degraded layer increases more rapidly within the first 3-4 years in the body. [104] This timing coincides with the median timing of mesh excision. [10] This indicates that changes of the polymer likely contribute to the mechanisms of complications.

For the mechanisms of degradation in vivo, it is known that oxidative substances expressed by macrophages and other chemical compounds in the tissue generate oxidative environment. [105] [89] Oxidation was determined as a mechanism of degradation in the earlier studies, that is why commercial products contain antioxidants. [89]

As for any substance, the breakdown invariably results in particles and simpler molecules, or chemical products of degradation. In vitro thermal degradation of polypropylene produces an array of organic molecules such as acids, ketones, ethers, aldehydes, alcohols and smaller hydrocarbons. [106] Thermal degradation is easier to study and, although the conditions are different from other types of degradation, it provides information of a range of possible chemicals that can be produced through other types of degradation, including in the body. Additionally, additives used to stabilize the polymer can also leach into the tissue. In published literature, additives leaching from polypropylene labware were shown to affect cultured cells in vitro. [107] In patients, a systemic effect was detected when intravenous injections of saline from prefilled and stored polypropylene syringes were found to induce smell and taste effects (metallic, chemical taste) in patients. This indicated that the substances leach into saline during storage, then enter blood and reach taste and smell receptors after injection. [108] [109] Larger scales and particles of degraded material also shed from the mesh fibers during their manipulations. They can be seen in the blood clot adherent to excised specimens and embedded in the tissue at sites of previous excisions. These scaled-off particles of degradation layer trigger the same foreign body type inflammation in the tissue as the original non-degraded fibers. For a systemic effect, chemical substances and small particles can travel through the blood stream but the overall burden and effect of this is not clear at this time.

Recently there was a study which, to my knowledge is the only study that concluded that the cracked layer is not degraded polypropylene. The used cleaning procedures were more extensive than those used by previous researchers. [110] The exposed surface may not have been the original surface as extensive cleaning could remove all detachable materials, including tissue residue and polypropylene degradation layer. After observing non-degraded polypropylene at the exposed surface, the authors concluded that the brittle layer is composed of proteins cross-linked

by formalin. This conclusion does not explain the fact that cracked layer can be seen immediately after mesh excision, without exposure to formalin. [111] It also does not explain presence of premanufactured granules of blue dye within the layer. The granules, as they are added to resin during manufacturing serve as an internal marker of polypropylene.

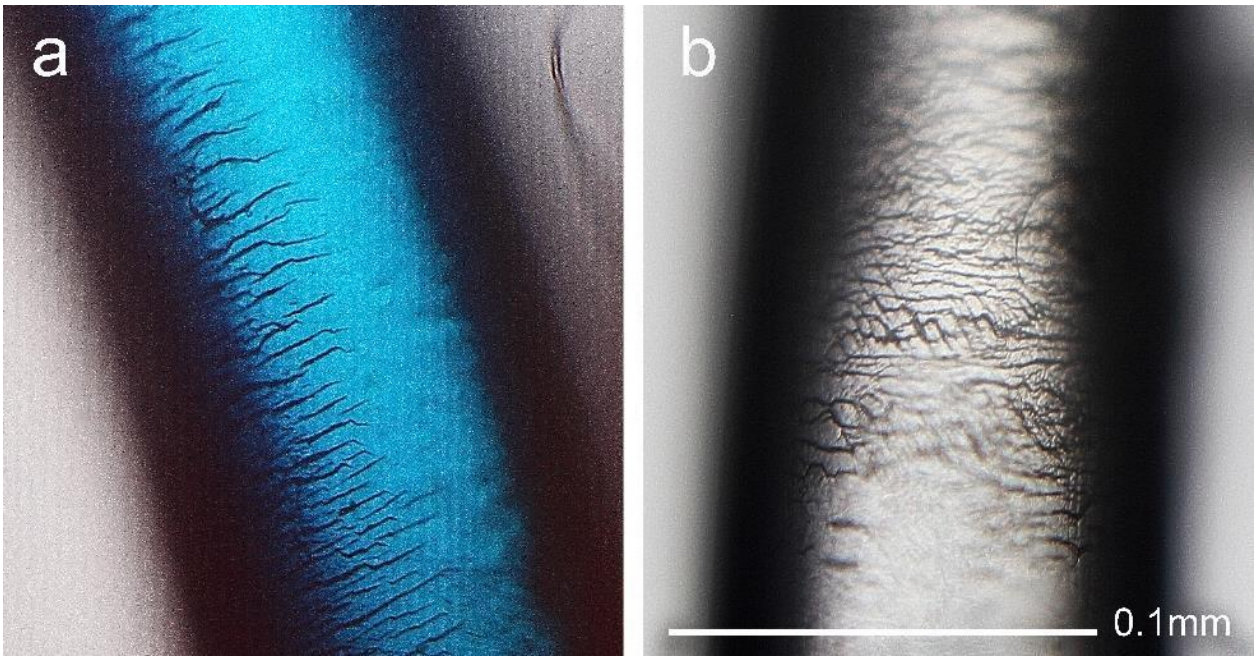


Figure 22. Surface cracking observed immediately after mesh excision, before exposing mesh fibers to any chemicals. [104]

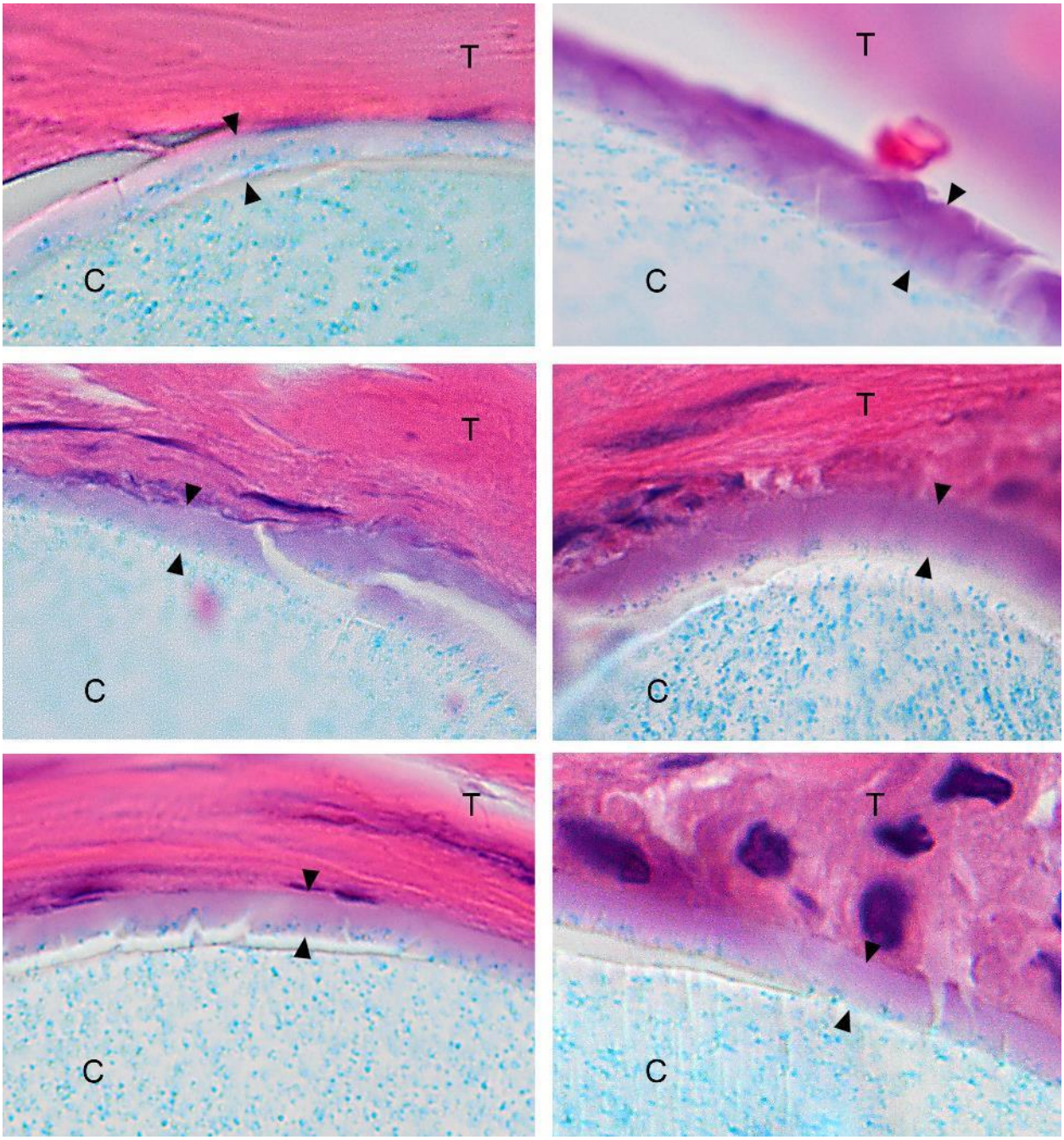


Figure 23. Retention of the blue granules in the degradation layer indicates its origin from polypropylene. [111] Blue granules are present in the fiber core (C) and in the degraded layer (between arrowheads).

Question 4:

Is there any consensus on ways to identify women for whom mesh is likely to be less successful? For example, physical characteristics, immunological responses, vaginal microbiomes.

Answer:

From a pathological point, the unifying cause of the complications is mesh as a foreign object. However, the mechanisms of complications are multifactorial. Based on what we learned for the last few decades foreign body type inflammation, scarring, mesh contraction, mesh folding, nerve involvement, mesh erosion/migration through tissues, and other factors that were discussed earlier play their roles in the mechanisms of complications. Most of these factors are non-specific, inherent to mesh as a foreign object. As any foreign object, it can damage tissues mechanically and triggers tissue reactions. Some of these factors are modifiable by mesh design and its physical characteristics. For example, scarring can be modified by pore size, while mesh stiffness can have both positive and negative effects. A stiffer mesh can damage tissues but at the same time is less prone to folding.

From my experience, the mechanisms of local (non-systemic) complications are mostly mechanical, mainly through direct tissue damage and distortion. The combination of contributing factors varies from patient to patient. For example, in some patients mesh may happen to gather into a ball or erode through the vaginal mucosa or into the bladder. In other patients mesh may be flat (monolayered) but there happened to be a more pronounced nerve damage in the mesh. These events appear to be random which poses a challenge for identification of a marker or a criterion to select patients at risk. We similarly struggle to identify patients at risk for side effects of medications. There are also some non-mesh related factors such as smoking, diabetes, concurrent procedures that can contribute to the inherent risks of the devices. Essentially, all patients with an implant are at risk for complications but we cannot predict in whom and when a combination of all factors can lead to a complication. Also, individual risks for each patient can change over time as our tissue become weaker and we may acquire diseases such as diabetes.

I cannot comment on the systemic (autoimmune- or fibromyalgia-like) symptoms as these are not diagnosed by pathological examination.

Question 5:

We have an international perspective here, with exposure to the EU and the US regulatory regimes, is there anything that you think should be added to either the pre-market or the post-market testing for implantable devices?

Answer:

As discussed in Question 1, full assessment of the risk/benefit ratio needs to be based on long-term data. The full range, severity and rates of complications can become apparent only many years after device introduction. To ensure safety of the patients during this time it needs to be a stepwise approach:

i. In vitro studies and animal studies.

ii. Analysis of similar devices on the market for:
   - Type of complications
   - How to screen for these complications to detect them earlier
   - Analysis of how long it takes for complications to accumulate and reach a relative plateau.

iii. Initial smaller clinical trials for patients in whom conventional treatments failed.

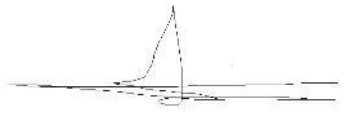
iv. After the devices showed a favourable predicted risk/benefit ratio and are cleared for sale there should be a continuous monitoring to collect real-life data in real-time. Since devices are permanent and it may take a long time for complications to become apparent, post-marketing surveillance is as important as the pre-marketing assessment. The best solution is nation-wide REGISTRIES with possibility of information sharing between countries. A public registry will have multiple benefits:
   - Independent - less risks for biases.
   - Comprehensive coverage of the full range of providers - real-life data.
   - Real-time monitoring can allow earlier detection of problematic devices and prevent further exposure of new patients to the risks.
   - Enforcement of mandatory reporting of all implantations, results, complications and subsequent treatments.
   - Standardization and accuracy of data collection. (For example, presently explanting surgeons may not know the type of excised device as patients change

providers over the years since implantation. Also, some providers may not be aware of the full range of possible complications.).

- Ability to standardize reporting of complication and cure/recurrence rates by a common time denominator. For example, in oncology 5- and 10-year survival rates are used for prognostication and comparison.
- Ability to update reporting for new, previously unexpected (unknown) symptoms in a standardised way.
- Ability to include long-term medications and other product types (injectable substances, tissue engineering etc.) to the registry since these are subject to the same problems of long-term complications as well as quality and heterogeneity of published information.

In fact, this review would not be necessary if nation-wide registries were implemented before introduction of the devices on the market. If collected properly, the data would have a better quality than in any presently available publication. The present discussion whether risks outweigh benefits (or vice versa) is because of the lack of high-quality long-term data.

Sincerely,



Vladimir Iakovlev, MD, FRCPC, FCAP DATE: October 04, 2019

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Professor Vik Khullar

Question 1:

Our patient groups have said to us that they feel synthetic mesh is unsuitable for long term insertion.

What are your views on this for the use of polypropylene mesh

- for stress urinary incontinence?

  It is suitable as there are patients for whom there is no other option.

  They must be appropriately counselled, patients with pre-existing diseases such as fibromyalgia, painful bladder, pelvic pain, recurrent urinary tract infections should not be treated or treated with extreme caution.

- for pelvic organ prolapse?

  only in a research settling

Is there such a thing as medical grade polypropylene? If so what is it?

I do not know

Question 2:

We are interested in understanding the physical properties of mesh once it has been inserted, including:

- shrinkage, Shrinkage is between 30 to 70% and is associated with subclinical bacterial infections.
- degradation, not known
- leeching of chemicals, and not known
- breakdown cause by body heat not known

Question 3:

What are your views on whether mesh degrades *in vivo*, and if so, how does it do so and what causes this?

No I do not believe that it breaks down in vivo. If as we do not see a weakening in tape over time.

Question 4:

Is there any consensus on ways to identify women for whom mesh is likely to be less successful? For example, physical characteristics, immunological responses, vaginal microbiomes. As in question 1
Question 5: We have an international perspective here, with exposure to the EU and the US regulatory regimes, is there anything that you think should be added to either the pre-market or the post-market testing for implantable devices? Premarket we need independent studies not commercially funded with appropriate follow up for a year and postmarketing surveillance for 5 years with a system which works

Professor Khullar also shared the following papers with the Review:

- Veit-Rubin, N, Tayrac, R, Cartwright, R, et al. Abnormal vaginal microbiome associated with vaginal mesh complications. Neurourology and Urodynamics. 2019; 38: 2255- 2263. https://doi.org/10.1002/nau.24129

- Derpaps, A, Digesu, GA, Panayi, D, et al. A persistent bladder erosion with ureteric involvement following mesh augmented repair of cystocele. American Journal of Obstetrics and Gynecology. 2010; 202(6): e5-e7

Dr Mark C Slack

Question 1:

Our patient groups have said to us that they feel synthetic mesh is unsuitable for long term insertion.

What are your views on this for the use of polypropylene mesh

- for stress urinary incontinence?
- for pelvic organ prolapse?

Is there such a thing as medical grade polypropylene? If so what is it?

This entire debate has to be conducted in the light of the available evidence. There is an extensive body of evidence supporting the use of mesh in pelvic organ prolapse repairs and for the treatment of urinary incontinence. The debate is much more sophisticated than trying to consider a binary response. As we have said on many occasions the factors that determine complications include:-

- *Type and construct of mesh eg multi vs monofilament*
- *Route of surgery in incontinence – retropubic (good)vs transobturator(bad)*
- *Route of surgery in prolapse – transvaginal vs abdominal(good)*
- *Use of fixation devices such as tackers*
- *Experience of surgeon – trained or not trained in urogynaecology. Inexperience is associated with higher complications*
- *Patient Factors- higher exposure in smokers, obese*

The literature supports good outcomes and very low complications in Retropubic tapes for incontinence with lower complication rates and equivalent outcomes than the non-mesh alternatives.

Transobturator and single incision mesh operations for incontinence have a higher complication rate than retropubic and anatomically pass through multiple muscle groups so cant be recommended

The literature also supports good outcomes and low complication rates for trans abdominal mesh procedures for prolapse (sacrocolpopexy and sacrohyteropexy) with lower complication rates than the non-mesh alternatives.

Transvaginal mesh procedures have not been shown to have better outcomes than non-mesh alternatives and therefore can not be recommended

The literature on complications from the HES data does not support the cataclysmic scenario suggested by the anti-mesh groups. It is also worth

remembering that more than 1.5 million mesh operations are performed annually for hernia repair since the late 90's and we have not seen the complications suggested by the lobby group.Even with only a 10% mesh complication rate that would be more than 3 million sufferers.

Question 2:

We are interested in understanding the physical properties of mesh once it has been inserted, including:

- shrinkage,
- degradation,
- leeching of chemicals, and
- breakdown cause by body heat

Mesh does not shrink. There is evidence that the mesh grafts shrink along with the natural shrinkage associated with would healing and scarring. This occurs in the cross-sectional area. There is no clear evidence of degradation, leeching of breakdown due to heat in the human studies. Some earlier studies that suggested this have been shown to have serious artefacts in the specimens caused by the process used for histological examination

Question 3:

What are your views on whether mesh degrades *in vivo*, and if so, how does it do so and what causes this?

There is no clear scientific evidence of degradation. Most explanted meshes are intact. It is also important to remember that the mesh would weigh about 2grams which as a proportion of body mass is negligible

Question 4:

Is there any consensus on ways to identify women for whom mesh is likely to be less successful?

For example, physical characteristics, immunological responses, vaginal microbiomes.

There is no robust scientific evidence of an immunological response other than the normal tissue reaction to a foreign body. This is modified by the construct of the mesh.

It is important to avoid mesh in smokers and the obese. Logic would also suggest that diabetics should be approached with caution.

My own work on the microbiome published in Science(see above) showed changes indirectly associated with subsequent changes. A multifilamentous mesh which is exposed in the vagina acts like a wick and draws vaginal fluid (with all the vaginal organisms)along its track. Once in other tissue these organisms then become pathological and infect the surrounding tissue and alter the vaginal microbiome. This response is not seen in monofilament meshes

Question 5:

We have an international perspective here, with exposure to the EU and the US regulatory regimes, is there anything that you think should be added to either the pre-market or the post-market testing for implantable devices?

I believe the recommendations set out by my group in the IUGA journal (see above) provides a framework for the safe introduction and subsequent surveillance of these products. A registry of implantable devices will further cement these steps.

One of the major problems was the marketing of these productys by companies to practitioners with insufficient surgical training or skills. It is essential that these operations be discussed at multidisciplinary meetings by people with the appropriate training and only performed by those with sufficient training.