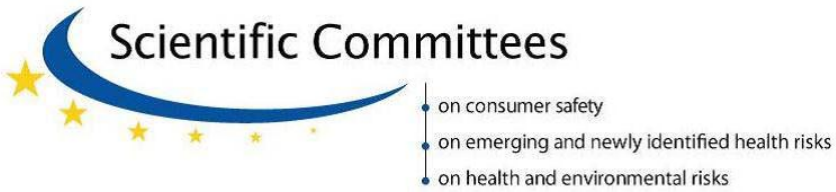
Scientific Committee on Emerging and Newly Identified Health Risks

SCENIHR

Preliminary Opinion on

The safety of surgical meshes used in urogynecological surgery



The SCENIHR approved this Opinion for public consultation by written procedure on 8 June 2015

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SCENIHR

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All Declarations of Working Group members and supporting experts are available at the following webpage:

http://ec.europa.eu/health/scientific_committees/emerging/members_wg/index_en.htm

1 ABSTRACT

Surgical meshes have been used since the 1950's to repair abdominal hernias and were then used in the 1990's for the treatment of male and female stress urinary incontinence (SUI), female pelvic organ prolapse (POP) and colorectal functional disorders (CFD). More recently the use of synthetic mesh and biological materials has become common requiring new surgical insertion tools and tissue fixation anchors.

The use of meshes in surgery has been shown to be associated with various adverse effects such as infection, tissue erosion, separation of vaginal epithelium leading to visualisation of the mesh (mesh exposure), mesh shrinkage and adverse side effects including pain and sexual dysfunction. The European Commission has thus requested the SCENIHR to assess the health risks of meshes used in urogynaecological surgery.

The various options for the treatment of pelvic floor dysfunctions were reviewed based on the scientific literature and the guidelines from scientific societies and health authorities. Included were both non-surgical and surgical treatment methods.

Non-biological surgical mesh materials can be divided into three categories: non-absorbable synthetics, absorbable synthetics, and composites. Synthetic meshes that have been used with mono- or multi-filament structure are usually classified according to their mesh size as Types 1, 2, 3 or 4 (Amid Classification) where type 1 is with pores >75 µm, type 2 with pores <10µm, type 3 with micropores and type 4 with monofilaments and nanopores <1µm. Today, type 1 polypropylene mesh is the most commonly used.

Clinical outcome following mesh implantation is influenced by material properties, product design, overall mesh size, route of implantation, patient characteristics, associated procedures (e.g. hysterectomy) and the surgeon's experience. The SCENIHR recommends that such aspects should be taken into account when choosing an appropriate therapy.

In assessing the risk associated with mesh application, it is important to consider the overall surface area of material used, the product design and the properties of the material used. The available evidence suggests a higher morbidity in treating POP, which uses a much larger amount of mesh compared to SUI.

When assessing synthetic mesh risks there is a need to clearly separate the smaller risks associated with SUI sling surgery from those of POP mesh surgery.

The implantation of any mesh for the treatment of POP via the vaginal route should be only considered in complex cases in particular after failed primary repair surgery. The use of autologous graft material is not feasible for POP because of the large mesh area required and the resulting donor morbidity. The use of absorbable mesh inserted either via a transabdominal or transvaginal route is associated with a high failure rate. Transvaginal surgery using non-absorbable synthetic mesh for POP involves a much greater surface area of mesh and is associated with a higher risk of mesh-related morbidity than seen with trans-abdominal insertion of this mesh. Colposuspension is associated with greater surgical morbidity.

In sling surgery, absorbable biological materials have been shown to have a high failure rate while sling surgery with non-absorbable synthetic mesh was effective with an approximately 4% mesh exposure rate at 5 years. Autologous slings are a more invasive alternative (because of the need to harvest native tissue) but they also can be inserted using a minimal invasive approach. The traditional surgical approach of colposuspension is associated with greater morbidity.

However, synthetic sling SUI surgery is an accepted procedure with proven efficacy and safety in the majority of patients with moderate to severe SUI, when used by an experienced and appropriately qualified surgeon. Therefore, the SCENIHR supports continuing its use for SUI, but emphahsises the importance of appropriately trained

surgeons and detailed counselling of patients about the associated risk/benefits.

Based on the available scientific evidence, the SCENIHR recommends that due to increased risks associated with the use of synthetic mesh for POP repair via a trans-vaginal route, this option should only be used when other surgical procedures have already failed or are expected to fail.

SCENIHR recommends limiting the amount of mesh for all procedures where possible. Based on the currently marketed products, assessment of the risks reported indicates that polypropylene type 1 meshes are the most appropriate synthetic meshes for vaginal use and polypropylene type 1 and polyester type 3 for insertion via the abdominal route. However, there is a need for further improvement in the composition and design of synthetic meshes, in particular for POP surgery.

The SCENIHR recommends the introduction of a certification system for surgeons based on existing international guidelines and established in cooperation with the relevant European Surgical Associations.

Appropriate patient selection and counselling is of paramount importance for the optimal outcome for all surgical procedures, particularly for the indications discussed. This should be based on the results of further clinical evidence, which should be collected in a systematic fashion for all of these devices.

Keywords: surgical meshes, risk assessment, Scientific Committee on Emerging and Newly Identified Health Risks

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1. EXECUTIVE SUMMARY

Stress urinary incontinence (SUI), which means incontinence occurring in association with exercise or rising intra-abdominal pressure, is a common condition in women, with its prevalence increasing with age. It occurs as a consequence of either weakness in the sphincter muscles within the walls of the urethra or prolapse of the urethra. Pelvic organ prolapse (POP), which can lead to prolapse of the urethra, can also lead to other consequences, such as prolapse of the vagina itself (anterior vaginal wall with bladder descent, and posterior vaginal wall with descent of the rectum and/or pouch of Douglas causing an enterocele and/or the uterus or vaginal vault). These conditions can be associated with SUI, overactive bladder (OAB), bladder outlet obstruction (BOO) symptoms and/or defaecatory disorders. Both SUI and POP are an important cause of reduced quality of life in the female population. Stress urinary incontinence is uncommon in men, for whom the most related health problems are commonly benign or, even more often, malignant prostate disease, which may require prostatic surgery. This type of surgery may result in incontinence as a direct consequence of damage to the urethral muscle controlling micturition.

The use of synthetic mesh has become popular in recent years for the management of SUI in female and, more recently, in male patients. It has also been employed in the management of pelvic organ prolapse in female patients, affecting both the lower genitourinary and colorectal tract. Review of the current literature and experience from clinical practice suggests that the use of surgical mesh in this context is associated with both benefits and risks. However, only a few randomised controlled studies have been published until now. The use of such mesh in repair surgery may lead to various complications of poor tissue integration, such as tissue erosion, exposure of the mesh and shrinkage of the mesh. The success of mesh interventions varies depending on the type of anatomical defect, its severity, the presence of risk factors, the rationale for the use of mesh and the skill and experience of surgeons.

In light of the above, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) was requested to provide a scientific Opinion on the safety of surgical meshes used in contemporary pelvic surgery. In the Opinion, the following issues have been addressed:

1. Risks associated with the use of surgical meshes for treating SUI and POP.
2. Identification of high-risk patient groups.
3. Risk of meshes other than for urogynecological surgery.
4. Need for further assessment in this field.
5. The scientific rationale for the use of synthetic surgical mesh for the management of urinary incontinence, POP and colorectal functional disorders.

Surgical meshes are produced by manufacturers to treat the above mentioned disorders and, because of their intended medical use, fall under the scope of the medical devices Directive 93/42/EEC (including Amendment 2007/47/EC). Among others this Directive contains essential requirements that medical devices must meet.

This Opinion reviews the options available for the management of SUI in female and male patients, and for the repair of POP affecting both the genitourinary and colorectal systems. The indication for the use of synthetic mesh is to provide additional support to the urethra, rectum or pelvic organs. In many cases, it is not possible to use patients' own tissue (autologous tissue) to provide this support, due to the lack of an adequate amount of tissue. In this context, in previous years, efforts to use materials either from human donors (allografts) or from animal sources (xenografts) have failed. This has added impetus to introduce synthetic mesh into clinical use.

Before a decision for surgery is made, it is important to explore non-surgical solutions for SUI, POP and colorectal functional disorders (CFD). If non-surgical solutions are unfeasible or unacceptable to the patient, in a shared decision process the surgeon and the patient must determine whether to use a surgical approach with or without mesh. Meshes are not the first choice for any indication, but are considered as a primary surgical solution in many cases of SUI, despite reported adverse events. For prolapse repair, larger meshes than for SUI are needed for vaginal or transabdominal implantation. In the context of POP, the use of mesh placed by the vaginal route is only recommended as a secondary choice after failed primary surgery. There is a limited use of mesh for CFD, mainly in specialised centres.

The scientific rationale for the use of synthetic mesh was reviewed based on contemporary literature. Several clinical implementation techniques are available and are briefly discussed in this Opinion. A number of adverse events are reported in association with the use of synthetic mesh which led to the creation of guidelines in recent years to provide advice on issues that require consideration before using synthetic surgical mesh. The choice to use synthetic meshes may influence the outcome of surgery and need to be discussed in detail with patients before carrying out surgery.

The following questions raised in the mandate are answered in this Opinion.

Are specific meshes, in terms of designs and/or materials, considered to be of a higher risk? If possible list and describe the risks.

There are a number of different types of meshes, which include:

- Allografts (e.g., cadaveric fascia, dura mater)
- Xenografts (e.g., porcine, bovine)
- Autografts (e.g., fascia lata, rectus fascia)
- Synthetic meshes (non-absorbable, e.g., polypropylene mesh)

In this Opinion the SCENIHR focuses on the use of synthetic non-absorbable meshes. These are usually classified in four types (see Table 8).

The current consensus is that synthetic non-absorbable meshes Type 2 (microporous, less than 10 microns, mono and multifilament) and Type 4 (sub-micronic and monofilament) are considered not appropriate for use in this clinical context.

Current evidence suggests:

- Type 1 (macroporous, monofilament) polypropylene is considered to be the most appropriate synthetic mesh for insertion via the vaginal route.

- Type 1 (macroporous, monofilament) polypropylene and Type 3 (microporous, multifilament) polyester are the most appropriate synthetic meshes for insertion via the abdominal route.

Currently, there is insufficient evidence on the performance, risk and efficiency of meshes of other materials.

In assessing the risks associated with surgical mesh insertion, it is important to consider the following:

- Overall surface area of material used (which is greater for POP than for SUI);
- Product design (e.g., physical characteristics of the mesh, size of the pore as a predisposing factor to infection in particular with a pore size of less than 75 microns);
- Material properties (biocompatibility, long-term stability, flexibility, elasticity, aging, etc.); mesh exposure is only seen with non- absorbable synthetic mesh;
- The physical properties and durability of the materials, balanced with the unwanted consequences of implanting the material on a long term basis.

Are certain surgical techniques of higher risk? If possible list and describe the risks.

All synthetic meshes are associated with the risk of mesh exposure as demonstrated by numerous animal studies. At two-year follow up it is also evident in 4% of patients.

In general terms, vaginal surgery is associated with a higher risk of mesh-related morbidity than abdominal insertion of mesh. However, the abdominal route is associated with specific increased risks related to the surgical approach, such as bowel occlusion. Furthermore, abdominal route requires general anaesthesia, whereas vaginal route is feasible also under spinal anaesthesia.

In risk assessment of the use of mesh it is necessary to differentiate between different indications such as SUI and POP.

The SCENIHR acknowledges the efficacy and use of implanted meshes for SUI in the majority of patients with moderate to severe SUI. It considers that the associated risk is limited, but recognises the absence of long-term data. Most complications associated with mesh insertion are related to the route of insertion.

The SCENIHR acknowledges that vaginally implanted mesh for POP is associated with increased risks compared to mesh implantation for SUI. Its use should be restricted to patients selected according to established evidence based clinical guidelines.

Are any combinations of the above (designs / materials and surgical techniques) of a higher risk?

Combination of the above mentioned designs/materials and surgical techniques may be associated with higher risk. With vaginal insertion of non-absorbable synthetic mesh a large surface area is associated with a higher complication rate compared with transabdominal insertion. However, there are generic differences and potential complications distinguishing the two surgical approaches, and this fact should also be taken into account in a risk assessment.

Are there specific limitations (e.g. clinical, designs / materials, surgical techniques) with the use of meshes in urogynecological surgery?

There are specific limitations with the use of meshes in urogynecological surgery. The following limitations apply:

- The available evidence suggests that the use of xenograft and allograft materials are associated with a high failure rate (due to degradation of mechanical properties with time) but are not associated with such severe side effects as of synthetic meshes.

- The risk of severe side effects (e.g. mesh exposure, shrinkage, pain) increases with the surface area of used synthetic non-absorbable meshes.

- Material properties will influence the outcome (biocompatibility, tissue integration, long-term stability, and mechanical responses over time including flexibility, elasticity and resistance to deformation).

- Patient characteristics, such as obesity will have an influence on efficacy and potential complications.

What are the risks of surgical interventions using mesh compared to classic surgical interventions?

When treating SUI, sling procedures are associated with more storage and voiding symptoms than other repositioning procedures. The use of synthetic non-absorbable mesh is associated with a risk of mesh exposure. However, other surgical procedures, such as colposuspension, are associated with an increased risk of long-term rectocele/enterocele.

When treating POP via the vaginal route, the use of synthetic non-absorbable mesh is associated with a risk of mesh exposure and *de novo* prolapse of the untreated vaginal compartment, as well as the development of *de novo* SUI. The risk of mesh exposure is reduced when using the transabdominal route compared to the transvaginal route.~~,~~ However, it should be keept in mind that transabdominal and tranvaginal POP repair have distinct indications as discussed in current guidelines. Moreover, there are generic differences and different potential complications for these two surgical approaches.

What factors could affect the outcome of the surgical interventions?

The factors influencing the surgical outcomes are:

- Material properties (biocompatibility, tissue integration, long-term stability, and mechanical performance over time which includes flexibility, elasticity, ageing and resistance to deformation)
- Product design (e.g. physical characteristics of the mesh, size of the pore as a predisposing factor to infection in particular with a pore size less than 75 microns)
- Overall mesh size (which is greater for POP than for SUI)
- Route of implantation, (e.g., vaginal or trans abdominal)
- Patient characteristics (e.g., age, obesity, smoking)
- Associated procedures (e.g., hysterectomy)
- Surgeon’s experience

The SCENIHR recognises the importance of following established guidelines, the need for adequate training and clinical experience of the surgeon as well as the need to further improve the design of the device, in particular for use in the pelvic floor, which appears to be a more demanding environment than the abdomen (where the non-degradable meshes have a lower complication rate).

Are there patients groups (e.g. in relation to age, weight or other comorbidities) for which the use of meshes would carry a specific risk?

Yes. The SCENIHR identifies the importance of the identification of high-risk patient groups. Age and obesity have been shown to be associated with increased risk of mesh exposure. This should be investigated further.

Thre are patients groups (e.g. in relation to age, weight or other comorbidities) for which the use of meshes would carry a specific risk. The SCENIHR acknowledges the importance of the identification of high-risk patient groups. For example, smoking is statistically associated with increased risk of mesh exposure. However, other factors such as age or obesity may also be important. This should be investigated further.

Taking into account the lack of long-term data on performance and safety of the use of synthetic non-absorbable mesh for POP repair, the SCENIHR recommends being cautious about using these in younger age groups.

In light of the above, identify risks associated with use(s) of meshes other than for urogynecological surgery and advise if further assessment in this field(s) is needed.

The SCENIHR notes there is limited information in the literature on this subject. There is a suggestion that morbidity may be associated with colorectal use of meshes. This needs to be quantified by further research before any conclusion can be made.

Recommendations

- Ensure the patients are correctly and comprehensively informed on the benefits and risks associated with the use of synthetic non-absorbable meshes.
- Establish European implant registries.
- Establish scientific studies to assess the long-term (at least 5 years) safety and performance of synthetic non-absorbable meshes.
- Encourage further research into novel design and materials, in particular absorbable meshes, and improved technologies for manufacturing meshes, such as electrospining.
- Encourage further research into the application of regenerative medicine technology, such as the cellular seeding of graft materials.
- Establish evidence-based European Guidelines.
- Develop training programs for surgeons in association with European medical associations.

2. BACKGROUND

Synthetic surgical meshes are medical devices intended to be implanted to reinforce soft tissues to treat their weakness, which include prolapse of the pelvic floor in women and weakness of the urethral sphincter in women and men.

According to the Council Directive 93/42/EEC, medical devices shall only be placed on the market if they meet the essential requirements laid down in the Annex I of the directive, in particular in relation to the health and safety of the patients.

Surgical meshes have been used since the 1950s to repair abdominal hernias. Implantable meshes have played an important role in the treatment of complex hernias and other abdominal wall reconstruction procedures. In the 1990s, gynecologists began using the same surgical mesh for surgical treatment of Stress Urinary Incontinence (SUI). The first procedure was called the "tension-free vaginal tape procedure" and was considered an alternative to the traditional surgery either using patients' own tissue or forming a hitch of the vagina and bladder base – a so-called colposuspension. The technique designed for the treatment of SUI involved a transabdominal or transvaginal approach, which subsequently evolved into a purely vaginal approach for the insertion of a loose mid-urethral sling procedure. Responding to the need perceived by the medical community, the medical devices manufacturers produced mesh kits containing the pre-shaped mesh implant(s) as well as the accessory tools needed for their placement. Surgical mesh kits continue to evolve using new materials and new insertion tools, tissue fixation anchors and surgical techniques.

Surgical mesh materials can be divided into four categories (1) non-absorbable synthetic, (2) absorbable synthetic (3) biologic (4) composite. Different types of designs are available aimed at better integration in the organism after implantation.

Pelvic floor dysfunction is a major health problem of women as they age, as shown by the 11.4% prevalence of symptomatic POP in women above 45 years (1 in every eight women) (Slieker-ten Hove *et al.*,2009), as well as the 11-20% (1 in every 5-10 women) lifetime risk of undergoing a single operation for pelvic organ prolapse or stress urinary incontinence at the age of 80 (Olsen *et al.*,1997, Wu *et al.*,2014). A large proportion of repeat operations (up to 1 in 3) has been documented as well as the time intervals between them, which decrease with each successive procedure.

Stress Urinary Incontinence (SUI) affects an estimated 20-40% of women. A Norwegian study (Hannestad *et al.*,2000) reported the percentage of patients with SUI to be approximately 50% with incontinence, the remainder with urge (11%) and mixed incontinence (36%).

The surgical repair of Pelvic Organ Prolapse (POP) proved to be a longstanding challenge with high failure rates of primary repair. As a consequence, clinicians changed to the use of substitute materials to augment the native tissue reaction including the use of developed mesh kits. The rapid and widespread transition from traditional pelvic organ prolapse surgery using native tissue, to mesh-augmented prolapse repair aimed to improve the frequent unsatisfactory outcomes.

Pelvic organ prolapse is a major health issue in women of older age and one of the most common indications for gynaecological surgery. Generally, the lifetime risk for a woman of undergoing surgical treatment for pelvic organ prolapse is about 7-20%. Despite the

fact that pelvic organ prolapse is one of the most common indications for gynaecologic surgery, epidemiological studies on incidence and prevalence are scarce (Slieker-ten-Hove *et al.,* 2009).

With the increasing life expectancy and the changing lifestyle of women, a further increase in the demand for pelvic floor surgery is expected for the future. This is already expressed in recent data on the lifetime risk for a woman to undergo a single operation for POP or SUI at the age of 80, which has been adjusted upwards from 11% in 1997 to 20% in 2014 (Wu *et al.,*2014). A vast group of women seem to prefer surgical correction of the vaginal anatomy.

Surgical meshes were introduced in recent years in the form of sling surgery used for the treatment of sphincteric incontinence in men usually following prostatic surgery.

Meshes have also been used for the treatment of colorectal prolapse. However, in the current Opinion this type of use is not dealt with specifically.

Current data suggest that the use of mesh in surgery is associated with benefits and risks, but there are few published randomised controlled trials. The use of mesh in repair surgery may lead to various complications, such as rejection, tissue erosion, mesh exposure and shrinkage. The rate of success of treatment with mesh implantation varies depending on the type of the anatomical defect, its severity, the presence of risk factors and the mesh used. Some women reported significant side effects after this type of surgery. Mesh complications in men are less commonly reported and are usually related to obstructive voiding.

3. TERMS OF REFERENCE

In light of the above considerations, the Scientific Committee on Emerging and Newly Identified Health Risks was requested to provide a scientific Opinion on "The safety of surgical meshes used in urogynecological surgery". The following items were addressed:

- Risks associated with the use of meshes in treating SUI and POP
  - Are specific meshes, in terms of designs and/or materials, considered to be of a higher risk? If possible list and describe the risks. (**Q1**)
  - Are certain surgery techniques of higher risk? If possible list and describe the risks. (**Q2**)
  - Are any combinations of the above (designs/materials and surgical techniques) of a higher risk? (**Q3**)
  - Are there specific limitations (e.g. clinical, designs/materials, surgical techniques) to the use of meshes in urogynecological surgery? (**Q4**)
  - What are the risks of surgical interventions using mesh compared to classic surgical interventions? (**Q5**)
  - What factors could affect the outcome of the surgical interventions? (**Q6**)
- Identification of high risk patient groups
  - Are there patients groups (e.g. in relation to age, weight or other comorbidities) for which the use of meshes would carry a specific risk? (**Q7**)
- In the light of the above, list risks associated with use(s) of meshes other than for urogynecological surgery and advise if further assessment in this field(s) is needed (**Q8**)

In its assessment the SCENIHR was invited to take into account the established registries in the field.

4. SCIENTIFIC RATIONALE

4.1. Introduction

4.1.1. Indications for the use of surgical meshes

Various options exist for the treatment of pelvic floor dysfunctions,. Treatment is justified, if conservative strategies, such as 'watchful waiting' or pelvic-muscle training (see 4.2.2) are unsuccessful. Depending on the type of pelvic floor dysfunction, the therapeutic approach and the size of mesh implanted may differ.

The indications and the risk/benefit ratios for the use of urogynecological meshes depend on the type of pelvic floor dysfunction. Currently, there are three major indications for which surgical meshes are used:

- Male and female Urinary Incontinence (UI)
- Female Pelvic Organ Prolapse (POP)
- Colorectal Functional Disorders (CFD)

Urinary incontinence (UI)

Female

About 50% of women with UI report symptoms of stress incontinence, but estimates of the prevalence and incidence are limited, because epidemiologic studies use inconsistent methods of measurement and different populations (Reynolds *et al.*, 2011) with regard to age and ethnicity. Longitudinal studies assessing the incidence and natural history of stress incontinence estimate an annual incidence of 4% to 10%. While remission does occur, data are sparse. Multiple risk factors are associated with developing the symptom of stress incontinence.

Male

Urinary incontinence in elderly community-dwelling men affects quality of life and increases the risk of institutionalisation (Shamliyan *et al.*, 2009). Pooled prevalence of UI increased with age to 21% to 32% in men above 60 years. Poor general health, comorbidities, severe physical limitations, cognitive impairment, stroke, urinary tract infections, prostate diseases and diabetes were associated with UI. Radical prostatectomy or radiotherapy for prostate cancer compared with watchful waiting increased UI. Short-term prevention of UI with pelvic floor muscle rehabilitation after prostatectomy was not consistently seen across randomised, controlled trials.

Pelvic organ prolapse

Pelvic organ prolapse (POP) is a highly prevalent condition that effects up to 50% of parous women, causing a variety of urinary, bowel and sexual symptoms that may be associated; however not all of those women are bothered by this condition. (Maher *et al.*, 2013). A large cross-sectional study among community-dwelling women between 45 and 85 years of age demonstrated a prevalence rate of 'symptomatic' POP of 11.4%.

However, only 6.9% of women with stage I and 15.8% of those with stage II experienced problems, e.g. vaginal bulge symptoms. (Slieker-ten-Hove *et al.*, 2009) Some loss of utero-vaginal support is present in most adult women and should be considered physiological (Milani, 2012). Surgery should only be considered if symptomatic POP is present and when conservative measures/therapy have failed (Dutch Multidisciplinary Guidelines on Prolapse, 2014).

Colorectal functional disorders

Internal or external rectal prolapse may be problematic and associated with constipation, obstructed defecation, faecal incontinence and pain. Treatment may be conservative (such as increased dietary fibre, pelvic physiotherapy) or surgical. For the surgical therapy of internal rectal prolapse, an open or laparoscopic anterior rectopexy is often performed. Synthetic mesh is used to suspend and distract the prolapsed part of the rectum. Some patients who have undergone this treatment report chronic pain. (Dutch Guidelines, 2014; Dutch Health Care Inspectorate, 2013).

4.1.2. Regulatory framework

Surgical mesh as a medical device

Surgical meshes are produced by manufacturers to treat female urinary incontinence, pelvic organ prolapse or colorectal functional disorders, and hence, because of their intended medical purpose, fall under the scope of the medical devices directive 93/42/EEC and amendment 2007/47/EC which contain the essential requirements of medical devices (Annex I), the conformity assessment procedure and the obligations of manufacturers for placing medical devices on the European market.

Apart from specific design-related requirements such as on biocompatibility, stability and usability, which include protection from foreseeable error, mistake and misuse, general requirements demand that a medical device must:

- have an acceptable risk/benefit ratio;
- be designed based on state-of-the-art knowledge by observing the principles of inherent safety;
- achieve the intended performance;
- must not compromise the clinical condition and safety of the patients during the entire product lifetime as defined by the manufacturer;
- must not be adversely affected by transport and storage;
- have risks from unintended side-effects limited to an acceptable level when weighed against device's benefits;
- be accompanied by all information required to use the device safely; and
- have been proven safe and effective by clinical evidence.

There is a large variety of surgical meshes with quite different performance characteristics related to:

- material (artificial or biologic);
- shape;
- dimensions;
- filaments;
- pore size;
- thickness;
- knitting patterns;
- ageing;
- erosion/exposure;
- biocompatibility;
- instantaneous mechanical properties, such as
  - elasticity,
  - stiffness, and
  - bursting strength.
- Time-dependent mechanical properties, such as
  - creep,
  - relaxation,
  - shrinkage,
  - degradation

In addition, mesh performance may critically depend on the directionality of the imposed mechanical load and/or how it was placed and fixed into the surrounding tissue.

At the time of writing, there are no specific product standards on national, European or international levels. The available national standard in France (AFNOR NF S94-801) is restricted to requirements of preclinical and clinical testing of vaginal reinforcement implants for stress urinary incontinence that requires that both preclinical and clinical studies be carried out before introducing any new implantable mesh, as well as the post marketing surveillance. There are only few general aspects related to product design covered by existing standards such as on biocompatibility (EN 10993-1 to EN 10993-20) or on bursting properties (EN 13938-1, EN 13938-2), however, a device-specific standard containing specific requirements on the device is still lacking, in particular with quantitative requirements, such as site-specific mechanical properties, material ageing and degradation, inflammatory response to the implanted materials (as demonstrated in animals), and minimisation of mesh erosion.

The conformity assessment procedure for the CE labelling offers the manufacturer a choice among several modules, which depend on the intrinsic risks of a medical device for its intended use under normal conditions.

To account for the different hazard potential of the large diversity of medical devices, manufacturers must classify their devices into one out of the four risk classes I, IIa, IIb and III based on device's intrinsic risks. This is done by applying 18 classification rules as set out in Annex IX of the MDD 93/42/EEC and explained in guidance documents such as MEDDEV 2.4/1.

The European Union's New Approach regulatory policy, as adopted in 1986 and implemented for medical devices by the related Directives among others, now offers the manufacturer the possibility to replace third-party testing even of critical devices by manufacturer's self-responsible conformity assessment based on his third-party certified quality management system.

Because synthetic surgical meshes are non-active, implantable and intended for long-term use, according to rule 8 of the MDD when lacking supporting pharmaceutical coating, they belong to conformity class IIb (otherwise class III). This means that surgical meshes must either pass a third-party EC type examination by a European Notified Body (according to MDD Annex III) and requires the manufacturer to implement a quality management system (according to either MDD Annex IV, V or VI) that is also certified by a European Notified Body, or, alternatively, manufacturers can choose to implement a full Quality Management System (QMS), which must be certified by a Notified Body. However, in the case of meshes no mandatory testing of the device and not even a third-party test of its design dossier is requested.

In case a medical device compromises the health and/or safety of patients or other persons in spite of its correct installation, maintenance and use, adequate measures need to be taken by manufacturers, Member States and the Commission to remedy existing non-compliances.

With regard to the involved procedures for all medical devices, conformity with the essential requirements must be based on a convincing clinical evaluation of available clinical data. In addition, manufacturers must implement a risk management process, which includes a post-market surveillance procedure with active and continuous feedback data acquisition, monitoring and risk assessment. Post market surveillance must include both monitoring of complaints and adverse events, in addition to a regular review and updates to the body of clinical evidence for the performance of the device. The results of this regular surveillance must be assessed for potential subsequent application of routine risk reduction activities (e.g. improved instructions for use) and additional risk reduction activities (e.g. design changes, physician's education and training). Evidence of this process is essential to ensure that the risk to benefit ratio for the device can be justified by a manufacturer.

Furthermore, any malfunction, deterioration in the characteristics and/or performance, inadequacy in the labelling or instructions for use of a medical device that might lead or might have led to a serious deterioration of patient's state of health or to his/her death, must be reported to competent authorities.

Therefore, with regard to these obligations, sufficient clinical data should be available for surgical meshes to allow adequate risk assessment and identification of problems with their design and/or their use.

4.2. Treatment

Before surgery, it is important to consider non-surgical solutions for SUI, POP and CFD with the patient.

If non-surgical options are not feasible, then the surgeon must decide whether to use a surgical approach without or with mesh, although currently, meshes are considered a primary surgical solution in many cases of stress incontinence. All surgical approaches have risk and despite reported adverse events, mesh use still plays a primary role in surgery for urinary stress incontinence. Larger surface area meshes are needed for vaginal and transabdominal implantation for prolapse repair. For POP, the use of meshes

is usually considered as a second choice after failed primary surgery. There is a limited use of mesh for CFD in specialist centres.

4.2.1. Treatment without using meshes

Stress urinary incontinence (SUI)

- **Female**

Non-surgical treatment

Guidelines from EAU (European Association of Urology), NICE / RCOG (United Kingdom), CNGOF (College National des Gynécologues et Obstétriciens Français) and AFU (Association Française d'Urologie) (France), ACOG (American College of Obstetricians and Gynecologist) and ACP (American College of Physicians) (USA) recommend first-line treatment with pelvic floor muscle training (PFMT) in women with SUI (Qaseem *et al.*, 2014; Fritel *et al.*, 2010; Smith *et al.*, 2013; NICE, 2013; Lucas *et al.*, 2013). Pelvic floor muscle training should be as intensive as possible. Weight loss is recommended for obese women with SUI (grade: strong recommendation; moderate quality evidence).

No treatment: Spontaneous resolution of symptoms: After 2-15 years follow-up, 2-30% of women with stress incontinence at any time appear to undergo spontaneous resolution of symptoms (Dolan *et al.*, 2003; Heidler *et al.*, 2007; Lifford *et al.*, 2008; Jahanlu *et al.*, 2008; Reynolds *et al.*, 2011; Fritel *et al.*, 2012). However, a reliable spontaneous resolution rate cannot be determined because population (age, menopausal status, etc.), follow-up duration and diagnostic criteria (cure or just improvement) differ considerably between published studies.

Pads: They are routinely used by women and, to a lesser extent, by men with incontinence (Brazzelli *et al.*, 2002).

Weight loss: Randomised clinical trials show that in overweight and obese women, weight loss (>5%) is associated with a decrease in the prevalence of SUI symptoms and in stress-incontinence episodes (Subak *et al.*, 2009; Wing *et al.*, 2010).

Medication: Meta-analyses showed that medication with duloxetine is associated with a significant decrease in incontinence episode frequency when compared to placebo (Latthe *et al.*, 2008; Li *et al.*, 2013).

Local estrogens: A meta-analysis showed that in post-menopausal women, there was some evidence that estrogens used locally (vaginal creams or pessaries) may improve incontinence (global urinary incontinence) (Cody *et al.*, 2012).

Pessaries - Intravaginal devices: RCTs showed that the use of an intravaginal devices / pessary is associated with a decrease in incontinence episode frequency when compared to no treatment (Ziv *et al.*, 2008; Cornu *et al.*, 2013).

Urethral inserts - Urethral devices: The efficiency of urethral inserts has been poorly investigated. They are rarely used.

Physiotherapy: Numerous techniques of physiotherapy have been reported and evaluated in the field of SUI. The main technique utilised is pelvic floor muscle training (PFMT).

A recent review of PFMT in a Cochrane meta-analysis showed that in women presenting with SUI, PFMT was associated with higher cure rates (56% vs 6%, RR 8.3, 95%CI 3.6-19.0) when compared to no treatment (Dumoulin *et al.*, 2014). No serious adverse events have been reported.

In addition to PFMT, adjunct physical therapies include:

- Biofeedback (BF)
- Electrostimulation
- Magnetic therapy
- Weighted vaginal cones
- Bladder training.

Surgical treatment without mesh

Surgical approaches comprise:

o Female

Colposuspension: Retropubic urethropexy: For this approach, several techniques are applied such as the Burch and Marshall Marchetti Krantz (MMK) techniques.

The Burch procedure is carried out by abdominal route (open or laparoscopy). For an open technique, a Pfannenstiel incision is performed.

The open retropubic colposuspension is the widely evaluated surgical technique for SUI. Open retropubic colposuspension is associated with high rates of objective and subjective cure rates, especially in the long-term (Lapitan *et al.*, 2012). After 5 years, approximately 70% of women were still symptom-free or no longer complained of incontinence.

Laparoscopic colposuspension is associated with similar cure rates of SUI when compared to open colposuspension, but with a lower risk of complications and shorter hospital stay (Dean *et al.*, 2009).

Needle suspension: Several techniques using needle suspension such as Stamey, Raz, Pereyraand Gittes procedures have been described, but currently are rarely used.

Pubovaginal slings: Autologous fascial slings: This procedure is usually performed via an abdominal route. The autologous sling is made of a strip of tissue from the abdominal rectus fascia or fascia lata.

Autologous fascial slings are associated with similar cure rates of SUI for women when compared to open colposuspension, but with a higher risk of post-operative complications (bladder outlet obstruction, need for self-catheterisation, etc.) (Rehman *et al.*, 2011; Albo *et al.*, 2007).

Urethral balloon: This technique is not recommended as a first line surgical treatment for SUI (EAU, 2014 Lucas *et al.*, 2013; Fritel *et al.*, 2010; Hermieu *et al.*, 2010).

Urethral injections: Injections of bulking agents seem to be associated with lower cure rates of SUI when compared to colposuspension or autologous slings (Pickard *et al.*, 2004).

Stem cell periurethral injections - Cell therapy: There is insufficient data concerning a periurethral stem cell injections (autologous myoblasts, muscle derived stem cells, autologous fibroblasts) that is supposed to treat intrinsic sphincteric deficiency (Aref-Abid *et al.*, 2013).

Artificial urinary sphincter (AUS): The artificial urinary sphincter (AUS) in women has not yet been widely used nor evaluated in RCT. This technique is not recommended as a first line surgical treatment for SUI (EAU, 2014; Lucas *et al.*, 2013; Fritel *et al.*, 2010; Hermieu *et al.*, 2010).

- **Male**

Urethral injections: No existing evidence indicates that bulking agents cure post-prostatectomy incontinence. There is weak evidence that bulking agents can offer temporary improvement in quality of life in men with post-prostatectomy incontinence (EAU, 2014).

Synthetic mesh or sling: Fixed slings are positioned under the bulbar urethra and fixed by a retropubic or transobturator approach. The tension is adjusted during surgery and cannot be readjusted postoperatively. Fixed male slings appear to be less effective for men with severe incontinence, previous radiotherapy, or previous urethral stricture surgery. Possible harms include voiding dysfunction, device erosion and chronic pain (EAU, 2014).

Adjustable male mesh slings allow for adjusting the tension postoperatively. Evidence is restricted to small case series with short follow-up. There is no evidence that adjustability of the male sling offers additional benefit over other types of sling (EAU, 2014).

Artificial urinary sphincter (AUS): Although the AUS is considered to be the standard treatment for men with SUI, the quantity and level of evidence for effectiveness is low. There have been no well-designed prospective RCTs. Non-randomised cohort studies suggest that primary AUS implantation is effective for cure and improvement of SUI in men, but may be less effective for men who have had pelvic radiotherapy.

There is no evidence that tandem cuff placement and insertion of the device through a single incision is superior to standard implantation (EAU, 2014).

Pelvic Organ Prolapse (POP)

Non-surgical treatment

No treatment: Without treatment, spontaneous regression of symptoms and/or anatomical status in women with POP is common, but a large prospective cohort study concluded that a small proportion of women with symptomatic POP had progression within 5 years (Miedel *et al.*, 2011; Bradley *et al.*, 2007).

Taking no treatment but following lifestyle advice may also have some effect. Obesity may be a risk factor for POP and for POP recurrence following surgery, e.g. other factors that increase intra-abdominal pressure (chronic heavy lifting, repetitive cough efforts, dyschezia/obstructive defecation syndrome). The prevalence of POP seems to be increased in women who report carrying out heavy lifting.

Being overweight or obese is associated with progression of POP. Weight loss does not appear to be significantly associated with regression of POP, suggesting that damage to the pelvic floor related to weight gain might be irreversible.

Pessaries: Using intravaginal devices offer an effective and patient-reported satisfactory treatment. However, side effects exist such as vaginal (anaerobic) discharge or incarceration. Regular review is required and the discontinuation rate is very high at long-term follow-up (Bugge *et al.*, 2013).

Physiotherapy: Pelvic floor muscle training should be the first line treatment for POP with or without pessary use, but the training needs proper instruction and close follow-up to be effective. PFMT is associated with a reduction in symptoms associated with POP and decrease in ICS (International Continence Society) POP-Q (POP Quantification system) stage 1/2 prolapse, although the clinical relevance of this improvement is not yet established. (Hagen *et al.*, 2014).

Medication: Whilst local oestrogen therapy can provide good symptomatic benefit, there is no evidence that it corrects the anatomical changes of POP. A recent Cochrane review concluded that there was limited evidence from randomised controlled trials regarding the use of oestrogens for the prevention and management of pelvic organ prolapse (Ismail *et al.*, 2010).

Surgical treatment without mesh

Cystocele repair: This procedure is done by the vaginal route (anterior colporrhaphy and vaginal, paravaginal repair). Anterior colporrhaphy is performed by an anterior vaginal wall incision in the midline, dissection to separate the vaginal epithelium from the underlying muscularis. This tissue is plicated in the midline using absorbable sutures. Recurrence rates are high, particularly using anatomic outcome criteria (i.e. POP stage 2 or higher). However when contemporary 'functional' outcome measures are used, that is (1) absence of bulge symptoms, (2) prolapse descent at or within the hymen, (3) absence of re-operation for POP, the success rate of this treatment at one year is reported at 88% (Chmielewski *et al.*, 2011) This stresses the importance of the selection

of clinically relevant outcome measurements. It is advisable to primarily use those that are important from a patient's perspective (Toozs *et al.*, 2012).

The objective of paravaginal repair by the vaginal route is to re-attach the detached lateral vaginal fascia to its 'normal' points of insertion on the lateral sidewall. There is very limited data about this technique (Maher *et al.*, 2013).

Rectocele repair: The technique of rectocele repair (posterior colporrhaphy and site specific posterior repair) by vaginal route consists in the correction of defects in the rectovaginal fascia separating rectum and vaginal mucosa (Maher *et al.*, 2013). A midline incision is performed on the posterior wall of the vaginal mucosa. The vagina is dissected from the rectum in the midline. In posterior colporraphy, the recto-vaginal fascia is approximated in the midline either with continuous or interrupted absorbable sutures.

Apical repair: The treatment of uterine prolapse or vaginal apical prolapse depends on the patient's characteristics (previous hysterectomy, concomitant hysterectomy) and the surgeon's policy. The treatment of uterine/apical prolapse consists in hysterectomy+colpopexy or hysteropexy or colpopexy (Maher *et al.*, Cochrane 2013). The 'pexy' (suspension) may be performed using sacrospinous or utero-sacral ligament suspension.

Results associated with sacrospinous or uterosacral ligaments seem comparable (Barber *et al.*, 2014).

Colpocleisis*:* Obliterative procedures such as colpocleisis (LeFort colpocleisis, colpohysterectomy, colpectomy) are offered to women with POP, who no longer wish to preserve vaginal coital function. The technique consists in vaginal closure +/- colpectomy or colpo-hysterectomy. Colpocleisis is associated with high success rates, low rates of recurrence and low rates of complications, especially after the age of 80 (Sung *et al.*, 2006; Fitzgerald *et al.*, 2008; Mueller *et al.*, 2014; Vij *et al.*, 2014; Zebede *et al.*, 2014).

Cystocele repair: Abdominal paravaginal repair via the abdominal route is performed through a Pfannenstiel incision (laparotomy) or laparoscopically. After entering the paravesical space and/or prepubic space, tears avulsing the pubocervical fascia from the arcus tendineus pelvic fascia (ATFP) are repaired by re-anchoring the detached anterior vaginal suspensory hammock to the pelvic girdle with interrupted non-absorbable or absorbable sutures (Reid *et al.*, 2011).

Isolated abdominal hysterectomy: Isolated abdominal hysterectomy has not been evaluated for the treatment of uterine/pelvic organ prolapse.

Uterine suspension with anterior fixation or posterior uterine suspension using non-absorbable sutures has been widely reported by laparotomy or laparoscopy (Smith *et al.*, 1977). The use of strips of skin (Poulhés *et al.*, 1971) or fascia lata (Ridley *et al.*, 1976) for uterine and bladder suspension has also been described.

Abdominal sacral hysteropexy/colpopexy: This procedure for uterine/vault prolapse uses mesh to secure the vagina up to the sacrum and is associated with a low complication rate (i.e., de novo dyspareunia and vaginal mesh exposure) because the vagina is not opened (Roovers, 2004; Maher *et al.*, 2004).

Abdominal uterosacral ligament suspension: The technique (colpopexy) consists of suspending the vaginal apex (mainly following concomitant hysterectomy) to the uterosacral ligaments, using non-absorbable or absorbable sutures, laparoscopically (Ostrzenski *et al.*, 1996; Filmar *et al.*, 2014) or by laparotomy (Cunjian *et al.*, 2012; Lowenstein *et al.*, 2009; Crigler *et al.*, 2012).However, Jeon *et al.* (2008) have shown that abdominal uterosacral ligament colpopexy (with concomitant hysterectomy) was associated with an increased risk of recurrence (6.2 times higher) when compared to abdominal sacral colpopexy with mesh and hysterectomy.

Anterior abdominal rectopexy: Some authors reported anterior rectopexy for rectocele repair without mesh for the treatment of rectocele (Pironi *et al.*, 2012).

Pelvic cul-de-sac (Douglas pouch) closure: This technique has not been evaluated for the treatment of uterine/pelvic organ prolapse as an isolated technique.

Colorectal Functional Disorders (CFD)

In the following, the various treatment options will only be briefly mentioned, as CFD only marginally falls within the scope of this Opinion and most approaches have been described in previous chapters.

No treatment - Spontaneous resolution of symptoms

- Weight loss
- Medication
- Pessaries
- Physiotherapy
- Pads - Plugs

Surgical techniques without mesh

- Artificial anal sphincter
- Abdominal route
- Vaginal route

- Perineal route
- Trans-anal surgery.

4.2.2. Treatment using meshes

The aim of using meshes

The rationale behind the use of synthetic meshes in urogynecological surgery was to increase the durability of surgical results, particularly with regard to recurrence of pelvic organ prolapse (POP) and/or urinary stress incontinence (USI), and to reduce re-operation rates of POP. Recurrence rates for using native tissues for these repairs is about 20-30% within 10 years of follow-up (Olsen *et al.*, 1997; Denman *et al.*, 2008).

For the vaginal repair of pelvic organ prolapse, synthetic materials have been used since the start of this millennium (absorbable mesh: polyglactin; Weber *et al.*, 2001). In 2004, a wide spread introduction of non-absorbable synthetic meshes started, particularly distributed in so-called 'mesh-kits' (synthetic polypropylene). It is unclear whether the use of these synthetic meshes/mesh kits has actually significantly reduced the rate of prolapse recurrence and/or re-operations for POP in the longer term. There are no scientific studies on long-term follow-up (e.g., 10 years) with randomised trials that compared the use of these mesh kits with native tissue repair. These data are urgently needed to quantify the risk/benefit ratio of these treatments/biomaterials for pelvic floor reconstructive surgery. However, authorities have been critical about the efficiency of synthetic meshes in their reports.

Introduction

Biological grafts are alternatives to synthetic mesh. Autologous fascia is the most commonly used material with over 100 years of experience and good efficacy for the treatment of SUI.. The main drawback, however, is the need to harvest the graft from a donor site (fascia lata from the thigh, or rectus fascia from the abdominal wall), and potential morbidity (e.g. wound infection, scar, nerve injury, hernia) (Birch and Fynes, 2002a). Additionally, there is a limitation on how much graft can be harvested. This precludes its use in POP, which is associated with relatively large fascial defects. These problems can be avoided by using grafts derived from cadavers or, alternatively, animal-derived collagen matrices (e.g., porcine dermis, porcine small intestine, bovine dermis). However, these materials require extensive processing (decellularisation, sterilization and cross-linking processes) to resist degradation (Freytes *et al.*, 2006). While decellularisation renders materials non-immunogenic, both sterilisation (mandatory) and decellularisation may critically degrade their biomechanical properties. Cross-linking to improve strength of biomaterials can provoke a persistent inflammatory response associated with excessive fibrosis (Vangsness *et al.*, 2003). Furthermore, there is the risk of viral or prion transmission (Birch and Fynes, 2002a). Although, clinical studies are limited, clinical experience indicates that all of these natural materials appear to be associated with graft failure in the medium-term due to the body's encapsulation and subsequent degradation of the materials with limited remodelling.

There are many factors that influence the response to biomaterials, which can be divided into 3 broad categories:

- (1) Chemistry and manufacture influences on physical properties (e.g. their mechanical properties (stiffness and strength, porosity and degradability).
- (2) Nature of the patient's immune response to the implanted biomaterials.
- (3) Surgical- and patient-specific factors (e.g. individual anatomy, co-morbidities).

Currently, there are several hypotheses describing implant failure: (a) mechanical failure of the material (i.e., the materials do not have the appropriate mechanical properties), (b) enzymatic degradation resulting in mechanical failure of the material and (c) chronic inflammation leading to fibrosis and erosion of the material through the host tissues.

Literature search on biomaterials

A literature search limited to the years 1990 to 2013 was performed using the MEDLINE database for studies investigating the *in vivo* response to biomaterials used routinely in pelvic floor surgery and clinical trials (Gigliobianco *et al.,* 2014). The following search terms were used: 'pelvis', 'pelvic floor', 'vagina', '*in vivo', 'in vitro*', 'biocompatibility', 'prolapse', 'incontinence', 'biomaterial', 'sling', 'mesh', 'polypropylene', 'autografts', 'allografts' and 'xenografts'. Abstracts were screened for relevance by two persons before full articles were retrieved. Papers were included if they described changes in physical or biomechanical properties of materials after implantation in animals or humans or the histological features of the host response to the implanted material. Implantation sites were restricted to subcutaneous, intravaginal or the abdominal muscles.

In examining the literature on meshes, the SCENIHR searched Medline for articles from 1990 to 2013 containing clinical and animal studies of pelvic floor repair materials and found 10 studies on autologous materials, 11 on allograft materials, 23 on xenografts and 30 on polypropylene meshes. These articles form the basis of the review included in the Opinion and are summarised in Appendices I-IV.

Autologous materials

Introduction

Autologous grafts harvested from the rectus fascia and fascia lata have long been used in SUI surgery. A major advantage of autografts over synthetic materials is that erosion is almost unheard of (Golomb *et al.,* 2001) and the overall long-term outcomes with autografts are largely excellent with reported rates of cure generally over 90% (Morgan *et al.,* 2000; Latini *et al.,* 2004). Possible disadvantages of autografts are that the connective tissues of patients with SUI may be inherently weak which pre-disposes them to failure and for pelvic organ prolapsed surgery, and it is necessary to harvest adequate amounts of tissue.

Biomechanical properties

In all four studies, there was agreement that the mechanical properties did not change significantly over 12 to 16 weeks duration (Choe *et al.*, 2001; Kim *et al.*, 2001; Dora *et al.*, 2004; Hilger *et al.*, 2006).

Host response

Eleven reported studies suggest that when autologous fascia is implanted, there may be a minimal to moderate inflammatory response, a moderate degree of collagen production and a suggestion that grafts undergo a degree of remodelling over the long-term (Dora *et al.*, 2004; Hilger *et al.*, 2006; Choe *et al.*, 2001; Kim *et al.*, 2001; FitzGerald *et al.*, 2000; Jeong *et al.*, 2000; Carneiro *et al.*, 2005; Krambeck *et al.*, 2006; Wooddruff *et al.*, 2008; Pinna *et al.*, 2011; Almeida *et al.*, 2007).

Allografts

Introduction

Allografts used in pelvic floor reconstruction usually consist of fascia. The donors are screened for infectious diseases before the grafts undergo cleaning, freeze-drying and gamma irradiation to eradicate any infectious or immunogenic material. A concern with these grafts is that the donors are often elderly with age-related connective tissue weakening (Moalli, 2006), and in addition, processing techniques such as freeze-drying and solvent dehydration may reduce tensile strength (Lemer *et al.*, 1999).

Cadaveric grafts are advantageous in that they avoid donor site complications. In terms of efficacy, results are mixed. Some have shown cadaveric fascia have similar subjective cure rates compared with autologous fascia at around 90% at 2 years (McBride *et al.*, 2005). However, upon urodynamic testing, 42% of cadaveric graft patients had SUI, whereas no patients with autologous grafts had SUI (Howden *et al.*, 2006). Five studies show disparate results (Hilger *et al.*, 2006; Kim *et al.*, 2001; Walter *et al.*, 2003; Spiess *et al*., 2004; Rice *et al.*, 2004)

Biomechanical properties

The available studies show disparate results with respect to the changes in mechanical properties of allografts following implantation which may be attributable to the heterogeneity in the type of allografts used, the animals studied, the sites of implantation and the assessment at different time points (REFERENCEs).

Host response

There have been many studies in which allografts have been implanted into animals and humans. The time since implantation ranged from 2 days up to 65 weeks (Hilger *et al*, 2006; Krambeck *et al.*, 2006; Woodruff *et al.*, 2008; Rice *et al.*, 2010; Sclafani *et al.*, 2000; Yildirim *et al.*, 2005; VandeVord *et al.*, 2010; Kolb *et al.*, 2012). Five of these report good integration into the abdominal wall (Scalfani *et al.*, 2000; Kolb *et al.*, 2012; Richters *et al.*, 2008) and rectus muscle (Rice *et al.*, 2010; Yildirim *et al.*, 2005) in different animal models. However others, such as Hilger *et al.*, 2006; Krambeck *et al.*, 2006; VandeVord *et al.*, 2010) have found relatively poor cell

infiltration and fragmentation of the scaffolds. Overall there was a degree of agreement that allograft induces an acute inflammatory response around the grafts (Hilger *et al.*, 2006; Krambeck *et al.*, 2006; Rice *et al.*, 2010; Sclafani *et al.*, 2000; Yildirim *et al.*, 2005; VandeVord *et al.*, 2010; Kolb *et al.*, 2012; Richters *et al.*, 2008).

Xenografts

Introduction

Grafts from animals, mainly porcine and bovine, have been used in pelvic floor surgery (references). These materials undergo extensive processing after harvesting to de-cellularise and render them non-immunogenic. Additionally, FDA regulations on animal source and vaccination status must comply (Amrute and Badlani, 2009). Porcine dermis may be artificially cross-linked using hexamethylene-di-isocyanate to make it more resistant to enzymatic digestion (Winters, 2006). Clinical studies showed lower continence rates for porcine dermis (approx. 80%) and increased re-operation than for synthetic tape or autologous fascia (Lucas M, 2004). Porcine small intestine submucosa (SIS) has cure rates from 79 to 93% at 2 and 4 year follow-up, respectively (Jones *et al.*, 2005; Rutner *et al.*, 2003). However, one study raised concerns that SIS may not be strictly acellular and may contain porcine DNA (Zheng *et al.*, 2005), which, if present, would lead to an aggressive immune response and destruction of the implant.

Biomechanical properties

Non-cross-linked porcine dermal collagen matrix is degraded rapidly (within 3 months) and loses most of its mechanical integrity within this period (references). By contrast, cross-linked porcine dermal collagen matrix is more resistant to degradation and maintains its mechanical properties for at least 3 months, whereas SIS appears to increase in strength after as long as 2 years after implantation (references). It is well known that the degree of cross-linking affects the inflammatory response to materials – a little is fine, but too much leads to an M1 macrophage response (references).

The issue of how crosslinking affects natural collagenous biomaterials has been addressed in various studies. Studies on non-crosslinked materials show moderate remodelling, but often very rapid degradation. In contrast, crosslinked xenografts are associated with relatively little cell infiltration, more remodelling and in some cases, encapsulation of implants. (Cole *et al.*, 2003; Badylak *et al.*, 2001)

Host response

There have been an extensive number of studies looking at the extent of the inflammatory response of the host to xenografts for example Hilger et al. and Pierce et al. found minimal neovascularization and collagen ingrowth in porcine dermal xenografts (Hilger *et al.*, 2006; Pierce *et al.*, 2009b). In contrast, non-cross-linked SIS leads to high collagen ingrowth with a moderate degree of remodeling and orientation and high neovascularization (Almeida *et al.*, 2007; Rice *et al.*, 2010; VandeVord *et al.*, 2010; Liu *et al.*, 2011; Konstantinovic *et al.*, 2005; Zhang *et al.*,

2003; Ko *et al.*, 2006; Badylak *et al.*, 2002; Poulose *et al.*, 2005; Rauth *et al.*, 2007). On the other hand, many studies agree in reporting a very rapid degradation of the SIS which is replaced by the host tissue [Liu *et al.*, 2011; Zhang *et al.*, 2003; Badylak *et al.*, 2001; Badylak *et al.*, 2002; Thiel *et al.*, 2005; Daly *et al.*, 2012; Suckow *et al.*, 2012). Only two studies reported an absence of host fibroblast infiltration and fibrotic tissue penetration without neovascularization for SIS implanted in rats (MacLeod *et al.*, 2005) and rabbits (Krambeck *et al.*, 2006). In humans, Cole et al. performed revision surgery on a patient who had developed a bladder outlet obstruction after SIS implantation and found that the implant had been encapsulated (Cole *et al.*, 2003). Nevertheless, other investigators, at 12 and 48 months, respectively, found that the SIS was replaced by native tissue in humans (Wiedmann *et al.*, 2004; Deprest *et al.*, 2010). In summary, most studies suggest that the degree of cross-linkage affects the rate of degradation and the degree of the inflammatory response of the host. Cross-linked collagenous matrices induce little cell infiltration, hence there is limited collagen remodeling and graft degradation. In non-crosslinked xenografts, cell infiltration was greater with a faster degradation rate and collagen production.

Polypropylene

Introduction

There is a range of synthetic polypropylene meshes, which are summarised in Table 8 (§8). They are classified as Amid Classification Types 1, 2, 3 or 4 according to their mesh size, where 1 is macroporous (>75 μm), 2 is less than 10 μm, 3 is microporous, and 4 is nanoporous (<1μm). Thus, a wide range of synthetic materials has been investigated for use in the treatment of SUI. These materials offer several advantages including lack of transmission of infectious diseases amd easy availability, as well as sustainable tensile strength due to their potential non-degradable nature (Gomelsky and Dmochowski, 2007). Mesh materials have been classified into 4 groups based on their porosity (microporous or macroporous) and filamentous structure (monofilament or multifilament) (Amid *et al.*, 1997). The initial clinical experience with a mid-type II (microporous/multifilament fibres, e.g. expanded PTFE), and III (macroporous and microporous/multifilament fibres, e.g., Mersilene) meshes was largely negative with excision rates of up to 30% for expanded PTFE (Weinberger and Ostergard, 1996) and erosion rates of 17% for Mersilene (polyester) (Young *et al.*, 2001).

A greater pore size is considered advantageous, as it allows the admittance of immune cells and greater collagen ingrowth into the construct (Birch and Fynes, 2002b). This is expected to reduce the risk of mesh infection and accelerate and enhance host tissue integration. Monofilament meshes are thought to reduce the risk of infection in comparison to multifilament meshes. The theoretical concern with the latter is that bacteria may colonise the sub 10 μm spaces between fibres, which are inaccessible for the larger host immune cells (9-20 μm)(Winters *et al.*, 2006). Today, an Amid-type 1 polypropylene mesh that is macroporous and monofilament is most commonly used (Slack *et al.*, 2006).

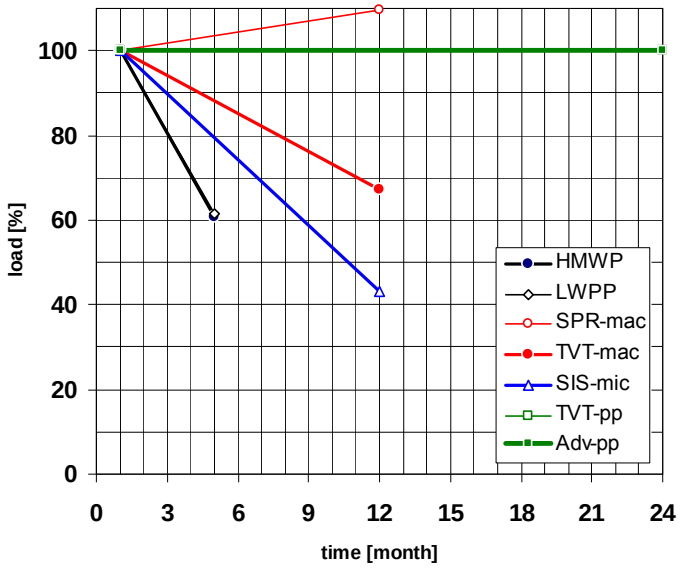
Polypropylene maintains its strength after implantation for up to 24 weeks (Spiess *et al.*, 2004; Zorn *et al.*, 2007; Bazi *et al.*, 2007). However, there is evidence that stiffness increases over time. (Melman *et al.*, 2011; Mangera *et al.*, 2012). There is some evidence that meshes with greater stiffness causes the surrounding tissue to weaken and affect turned stress shielding (Feola *et al.*, 2013). This may be compared to the effect of metal implants on the surrounding bone after orthopaedic surgery and could lead to thinning of the surrounding vaginal tissues and predispose erosion.

Biomechanical properties

Seven studies investigated the mechanical properties of polypropylene meshes with implantation times ranging from two weeks up to two years in animal models. Animal models used were rats abdominal wall (Spiess *et al.*, 2004; Zorn *et al.*, 2007), pig pre-peritoneal implantation (Boukerrou *et al.*, 2007), rat rectus fascia (Bazi *et al.*, 2007), mini-pig hernia repair (Melman *et al.*, 2011) and ewe abdominal and vaginal walls (Manodoro *et al.*, 2013).

Melman et al., (2011) tested Bard®Mesh, a knitted monofilament mesh made of High Molecular Weight Polypropylene (HMWPP) and Ultrapro®, a knitted macroporous composite mesh made of Low Molecular Weight Polypropylene (LMWPP) and polyglecaprone (§8, Table 8). They were implanted in a mini-pig hernia repair model for up to 5 months ( ). HMWPP decreased from 59.3 N maximal load at failure at 1 month to 36.0 N at 5 months, while LWPP mesh decreased from 61.5 to 37.8 N at 5 months (Melman et al., 2011). Long-term studies were carried out by Zorn et al.,(2007) where TVT and SPARC were compared to SIS in a rat abdominal wall defect for up to 12 months. Both TVT and SPARC are macroporous meshes made of polypropylene monofilaments. SPARC did not change its mechanical properties after 12 months of implantation (maximum load mass at baseline 4.44 N, at 12 months 4.88 N). By contrast the maximum load for TVT decreased from 7.64 N to 5.13 N for TVT and for SIS decreased from 3.94 N to 1.71 N (Zorn et al., 2007). Bazi et al.,also showed how similar the mechanical properties of Gynecare TVT and Advantage® are. Both are macroporous polypropylene monofilament meshes compared to other meshes such as IVS Tunneller, multifilament polypropylene mesh and SPARC. The lowest, at 25.2 N was TVT and the highest, 34.9 N was Advantage®, with no difference between them 24 weeks after implantation in rats rectus fascia (Bazi et al., 2007). Other studies agree with these parameters, where TVT complied with the highest break load (7.26 N), compared with 3.83 N for fascia lata up to 12 weeks after implantation in rat abdominal wall (Spiess et al., 2004), and was apparently less stiff than other synthetic materials used for meshes (0.23 N/_mm compared with Nylon, 6.83 N/mm) (Dietz et al., 2003).

Figure 1: Relative degradation of mechanical strength of synthetic meshes with implantation time



A recent study compared two sizes of meshes implanted in two different sites in a sheep model. Gynemesh was cut into two sizes (50x50 mm and 35x35 mm) and implanted in 20 adult ewes on the abdominal and vaginal walls for 60 and 90 days. After 90 days, grafts of both dimensions implanted on the vaginal wall were stiffer than those implanted on the abdominal wall (Manodoro *et al.*, 2013).

Physical characteristics of the mesh, such as monofilament or multifilament, porosity and polymer molecular weight, hugely affect the mechanical performance of the implants *in vivo*. shows that except for polypropylene meshes, the degradation of mechanical strength can be dramatic for most meshes.

Host response

Twenty-one papers addressed the host response to polypropylene meshes, which were assessed in rat abdominal wall (Klinge *et al.*, 2002; Zheng *et al.*, 2004; Konstantinovic *et al.*, 2005; Thiel *et al.*, 2005; Spelzini *et al.*, 2007; Zorn *et al.*, 2007), rat rectus fascia (Yildirim *et al.*, 2005; Bogusiewicz *et al.*, 2006; Bazi *et al.*, 2007), rabbit bladder neck (Rabah *et al.*, 2004), rabbit abdominal wall (Pascual *et al.*, 2012), rabbit rectus fascia (Krambeck *et al.*, 2006), rabbit vaginas (Huffaker *et al.*, 2008; Pierce *et al.*, 2009b), mini-pig hernia, (Melman *et al.*, 2011), pig peritoneum (Boulanger *et al.*, 2006; Boukerrou *et al.*, 2007), ewe vagina (de Tayrac *et al.*, 2007; Manodoro *et al.*, 2013), ewe abdominal wall (Manodoro *et al.*, 2013) models and in a few clinical studies (Falconer *et al.*, 2001; Wang *et al.*, 2004; Woodruff *et al.*, 2008; Elmer *et al.*, 2009). Studies focused on acute inflammatory responses to the most commonly used, non-degradable meshes, as described in Table 8 (§8). A few investigators studied the acute inflammatory response occurring from the day of implantation up to 30 days (Klinge *et al.*, 2002; Zheng *et al.*, 2004; Konstantinovic *et al.*, 2005; Thiel *et al.*, 2005; de Tayrac *et al.*, 2007; Spelzini *et al.*, 2007; Pascual *et al.*, 2012). Other studies addressed the immediate response at 1-3 months post implantation (Rabah *et al.*, 2004; Bogusiewicz *et al.*, 2006; Boulanger *et al.*, 2006; Krambeck *et al.*, 2006; Boukerrou *et al.*, 2007;

Huffaker *et al.*, 2008; Manodoro *et al.*, 2013) and long-term responses (>3 months) in which fibrosis and chronic inflammation are seen (Falconer *et al.*, 2001; Wang *et al.*, 2004; Bazi *et al.*, 2007; Zorn *et al.*, 2007; Woodruff *et al.*, 2008; Elmer *et al.*, 2009; Pierce *et al.*, 2009b; Melman *et al.*, 2011).

A recent study of Manodoro *et al.* ,(2013) showed at 90 days from implantation that 30% of Gynemesh grafts (50x50 mm) implanted in ewes caused vaginal erosion and exposure and 60% of the smaller Gynemesh meshes (35x35 mm) had a reduced surface (i.e., contraction) (Manodoro *et al.*, 2013).

Falconer *et al.*, showed that biopsies stained with Masson's Trichrome following Prolene and Mersilene meshes induced a higher inflammatory response in Mersilene compared with Prolene, which only triggered a small inflammatory reaction (Falconer *et al.*, 2001).

In a long-term study, Pierce *et al.*, (2009b) compared biological and synthetic grafts implanted in rabbits and found that Polypropylene caused a milder inflammatory reaction compared with a more long-term model with better host tissue incorporation compared to natural grafts. Furthermore, Bazi *et al.*,(2007) evaluated biopsies for inflammatory infiltrates, fibrosis, mast cells, muscular infiltration and collagen filling of the mesh on an arbitrary scale described as low, moderate or extensive in H&E, periodic acid-Schiff and toluidine blue stained tissue. This study concluded that all of the investigated materials (Advantage, IVS, SPARC and TVT) induced inflammation and collagen production, with SPARC having the mildest response while TVT was associated with the highest adverse responses (Bazi *et al.*, 2007). In another study, Elmer *et al.*, reported an increase in macrophages and mast cells and a mild, but persistent foreign body response to polypropylene meshes (Elmer *et al.*, 2009) which was consistent with other reports in which polypropylene meshes were invaded with macrophages and leukocytes, inflammatory infiltrates and collagen production (Pascual *et al.*, 2012; Pierce *et al.*, 2009b; Woodruff *et al.*, 2008; Bazi *et al.*, 2007; Bogusiewicz *et al.*, 2006; Yildirim *et al.*, 2005).

In summary, polypropylene meshes provoke pronounced inflammation, leading to a massive cell infiltration into the scaffold and ultimately induce collagen production (Govier *et al.*, 2004; Rabah *et al.*, 2004; Wang *et al.*, 2004; Bogusiewicz *et al.*, 2006; Bazi *et al.*, 2007; Maia de Almeida *et al.*, 2007; Huffaker *et al.*, 2008; Woodruff *et al.*, 2008; Elmer *et al.*, 2009; Pierce *et al.*, 2009a).

Post implantation changes and clinical outcomes

Biomechanics

In general, when biological materials fail it is due to enzymatic degradation post implantation, leading to a loss of mechanical support and weakening of the repair which is particularly evident with non-crosslinked xenogenic matrices. Chemical cross-linking appears to prevent degradation and improve mechanical outcomes. However, there is a lack of clinical evidence on the correlation between these mechanical outcomes and patient outcomes. Autologous grafts are the most successful biological material used in contemporary practice and the reviewed studies support long-term mechanical integrity. Nevertheless, there are several important limitations related to harvesting from the donor site, though the use of cadaveric tissues avoids these limitations. However, quality depends on the age and co-morbidities of the donor and this may explain diverse

mechanical properties of the grafts and is consistent with clinical studies showing poorer cure rates for cadaveric compared with autologous grafts.

Studies on long-term stability (24 months following implantation) showed that polypropylene meshes maintained their morphology and strength (Spiess *et al.*, 2004; Zorn *et al.*, 2007; Bazi *et al.*, 2007) but were associated with increasing stiffness (Melman *et al.*, 2011; Mangera *et al.*, 2012). Although this is consistent with durable cure rates particularly in SUI surgery, there is still doubt regarding efficacy of trans-vaginal POP repair, compared with native tissue repair. The major issue with polypropylene meshes are the associated serious complications, in particular, vaginal or urinary tract exposure (up to 10-14%) and because of greater stiffness, the surrounding tissue weakens, which is termed stress shielding (Feola *et al.*, 2013). This adverse effect can be compared to the effect of metal implants on the surrounding bone after orthopaedic surgery (Mahon *et al.*, 2012) and may lead to thinning of the surrounding vaginal tissues predisposing to erosion.

Host response

Implanted biomaterials may generate foreign body responses with some materials inducing an M1 macrophage response as a part of constructive remodelling which appears with some biological matrices, such as SIS. With materials which the body cannot remodel or integrate such as polypropylene meshes, the response is an aggressive M2 macrophage response (Remes and Williams, 1992; Wolf *et al.*, 2014).

Constant inflammation in some patients in response to some non-degradable materials may occur which leads to an up-regulation of degradative enzymes that do not degrade the material, but may damage the surrounding extracellular matrix and contribute to tissue thinning and mesh exposure. Moreover, perpetuation of the inflammatory response may cause activated fibroblasts to produce excessive disorganised collagen around the implant (i.e., fibrosis) which then encapsulates the material. A small amount of fibrosis is arguably advantageous for the repair in SUI, providing a stable back stop allowing urethral compression. However, excessive fibrosis may lead to mesh contraction resulting in increased pull on adjacent tissues leading to complications such as voiding dysfunction, pain and painful intercourse. In POP, this excessive fibrotic response may lead to mesh exposure, which presents a major reconstructive surgical challenge, often necessitating repeat procedures with no guarantee of symptom resolution. Nevertheless, because the vast majority of patients do well with mesh (reference), some degree of fibrosis may be helpful, whereas excessive fibrosis is detrimental.

Implantation of autologous fascia, in general, integrates well within host tissues and is associated with minimal inflammation when compared to polypropylene meshes with a degree of graft remodelling in human studies (Konstantinovic *et al.*, 2005; Rabah *et al.*, 2004). Notably, these human studies reported reoperative cases of clinical failure. Therefore, it is difficult to speculate whether successful outcomes result in fully integrated and remodelled graft. Non-cross linked xenografts are associated with clinical failure due to rapid degradation. The degradation, in any case, is presumably faster than the time it would take strong tissues to regenerate if no graft were done (Jeong *et al.*, 2000; Hilger *et al.*, 2006; Maia de Almeida *et al.*, 2007). Cross-linked grafts avoid this problem, but similar to synthetic mesh, they are associated with constant inflammation because the body is unable to integrate and remodel them and ultimately leads to graft encapsulation. Taken together, these data suggest that there is a need for a balance

between degradation and replacement by new host tissues with xenografts for which SIS appears to fulfil.

The immune response to a foreign material may be complex, dynamic and patient-specific. Polypropylene meshes provoke minimal adverse reaction when implanted in the abdominal wall for hernia repair, but are associated with complications in the pelvic floor and suggests a site-specific host response to biomechanical exposure (Patel *et al.*, 2012), which was confirmed in ewes (Manodoro *et al.*, 2013) and emphasises the need for relevant animal models and in long-term studies (Deprest and Feola, 2013).

Synthetic material such as polypropylene includes additives such as softeners like Bisphenyl-A (BPA), which may leak into tissue and cause adverse health effects (see SCENIHR Opinion on BPA), but since quantitative data on exposure are lacking, it is not possible to do a risk assessment. However, data on polypropylene implants for abdominal hernia repair suggest that there is no such safety concern (e.g. Henniford *et al.* 2000). In this study of 407 patients a satisfactory hernia repair was achieved in 98.1% of patients and the complication rate (mostly.

Implantation techniques for SUI

o Female patients

Implantation techniques of mid-urethral slings (MUS)

Retropubic (RP) approach (bottom-to-top and top-to-bottom)

MUS are placed by vaginal route through the retropubic space using a specific device/needle and/or exteriorised through the abdominal skin using two millimetre incisions. Two techniques, bottom-to-top and top-to-bottom are used and associated with complications such as bladder injury (6%), retropubic haematoma (<1%), iliac vessel injury (<1%), bowel inure (<1%), bladder outlet obstruction (BOO) (10%) that may require re-intervention for sling section (1%), vaginal sling exposure (1%), failure at short-term follow-up (10%) and recurrence at long-term follow-up (10%) (Ogah, 2009; Schimpf *et al.*, 2014).

Trans-obturator (TO) approach (out/in and in/out)

MUS are placed by vaginal route through obturator foramen (obturator and adductor muscles) using a helicoidal specific device/needle and exteriorised through the groin area skin using two millimetre incisions. Two different techniques including the inside-outside and outside-inside are associated with complications such as groin/hip/thigh pain (10%), urethral or bladder injury (1%), vaginal injury (1%), obturator haematoma (<1%) and bladder outlet obstruction (BOO) (10%) that may require reintervention for sling section (1%), vaginal sling exposure (1%), failure at short-term follow-up (10%) and recurrence at long-term follow-up (10%) (Ogah, 2009; Schimpf *et al.*, 2014)

Prepubic approach

MUS are placed by vaginal route through a subcutaneous perineal route. This approach was less investigated, but seems to be associated with lower cure rates (Daher, 2013; Long, 2013; Fritel *et al.*, 2010).

Single incision slings (SIS)

The risk of iliac vessel / bowel injury associated with RP approach and the high prevalence of groin pain associated with the TO approach have led to the development of a new generation of MUS: the 'mini-slings' in which a single incision is made. The sling is significantly shorter in length compared with 'classical' RP or TO slings. However, there are no data regarding the actual length of the implanted sling compared with standard ('classical') RP and TO MUS procedures. The SIS is placed by vaginal route, following a RP or a TO way, but the sling is not trans-cutaneously exteriorised (the insertion stops short of the obturator membrane). Huge differences in fixation mechanism of these SIS may influence outcomes (cure and complications rates). This less invasive technique is supposed to decrease complication rates, but the shorter length of the sling may be associated with lower cure rates, especially at long-term follow-up. Some SIS are partially 'adjustable' (per-operative adjustment), which makes it possible to adjust the tension of the fixing system.

An updated systematic review and meta-analysis of randomised controlled trials (RCTs) was recently performed comparing single-incision mini-slings (SIMS) versus standard mid-urethral slings (SMUS) in the surgical management of female stress urinary incontinence (SUI) (Mostafa *et al.,* 2014).

A literature search was performed for all RCTs and quasi-RCTs comparing SIMS with either transobturator tension-free vaginal tape (TO-TVT) or retropubic tension-free vaginal tape (RP-TVT). The literature search had no language restrictions and was last updated on May 2, 2013. The primary outcomes were patient-reported and objective cure rates at 12 to 36 months follow-up. Secondary outcomes included operative data; peri- and post-operative complications and repeat continence surgery. Data were analysed using RevMan software. Meta-analyses of TVT-Secur vs. SMUS were presented separately as the former was recently withdrawn from clinical practice.

A total of 26 RCTs (*n*=3308 women) were included. After excluding RCTs evaluating TVT-Secur, there was no evidence of significant differences between SIMS and SMUS in patient-reported cure rates (risk ratio [RR]: 0.94; 95% confidence interval [CI], 0.88–1.00) and objective cure rates (RR: 0.98; 95% CI, 0.94–1.01) at a mean follow-up of 18.6 months. These results were derived by comparing SIMS versus TO-TVT and RP-TVT separately. SIMS had significantly lower postoperative pain scores (weighted means difference [WMD]: −2.94; 95% CI, −4.16 to −1.73) and earlier return to normal activities and to work (WMD: −5.08; 95% CI, −9.59 to −0.56 and WMD: −7.20; 95% CI, −12.43 to −1.98, respectively). SIMS had a non-significant trend towards higher rates of repeat continence surgery (RR: 2.00; 95% CI, 0.93–4.31).

This meta-analysis showed that, excluding TVT-Secur, there was no evidence of significant differences in patient-reported and objective cure between currently used SIMS and SMUS at midterm follow-up while associated with more favourable recovery time. Results should be interpreted with caution due to the heterogeneity of the trials included.

Other MUS procedures

- Intermediate length slings

In an effort to maintain efficacy while reducing some side effects, manufacturers developed hybrid procedures using shorter slings (12 cm), that are placed using a classical TO placement technique (Waltregny *et al.*, 2012; de Leval *et al.*, 2011).

However, larger sample sized RCT and long-term follow-up are required before drawing conclusions.

- Adjustable MUS (post-operative adjustment)

No RCT has assessed adjustable MUS.

- **Male patients**

Implantation techniques of slings

Although numerous treatment options for male SUI exist, including penile clamps, transurethral bulking agents, or catheters (condom or indwelling), the most commonly utilised surgical therapies performed include placement of a male sling or AUS.

Since its initial introduction, the male sling has become increasingly utilised in cases of low-to-moderate volume (1–3 pads/day) incontinence. Although several variations of the male sling are currently available, the three subtypes with the most reported series available include the bone anchor sling (BAS), retro-urethral transobturator sling (RTS) and the adjustable retropubic sling (ARS).

Bone-anchored slings result in compression to the bulbar urethra through placement of a synthetic or organic mesh, which is secured to the inferior pubic ramus using six titanium screws. Sutures are subsequently secured to the screws and mesh material and tightened to result in appropriate tensioning. Following initial reports of degradation of organic materials, synthetic mesh has become the most commonly utilised material with the BAS (Dikranian *et al.*, 2004).

A second category of available male slings includes the RTS. In contrast to the BAS, which utilises anchored sutures, the RTS is self-anchored with bilateral polypropylene mesh arms placed in a transobturator fashion. The sling portion is secured at the proximal bulbar urethra with continence achieved through subsequent elevation of the urethra.

Several studies examined preoperative characteristics, surgical techniques and postoperative management principles that have been associated with improved outcomes with RTS placement (Soljanik *et al.*, 2012; Render *et al.*, 2009; Elzevier and Cornel, 2010). Predictive preoperative characteristics of worsened outcomes include weakened residual sphincter function, incomplete sphincter closure and lack of elongation of the coaptive sphincter zone. Intraoperative and postoperative factors associated with improved outcomes include tunnelling of the sling arms into subcutaneous tissues to improve fixation, placing five or more stitches, using non-absorbable stitches and minimising postoperative activity to reduce dislodgement.

Similar to RTS, ARS are surgically placed at the proximal bulbar urethra, with traction sutures placed retropubically. The sutures are then tensioned at the level of the rectus fascia utilising either a 'veritensor' device or silicone columns and washers to provide an appropriate level of urethral compression.

A fourth category of sling, which was recently introduced, is the quadratic sling. The sling consists of a broad-based mesh material placed over the bulbar urethra similar to the BAS. It is then self-secured with four mesh arms, which are placed in both a

transobturator (two arms) and prepubic (two arms) manner. The limbs may then be further secured to create additional points of fixation as needed.

The hypothesised mechanism for improved continence with the various sling designs varies and is not thoroughly understood. Bone-anchored slings likely achieve direct compression of the bulbar urethra with subsequent increases in outflow resistance. In contrast, the mechanism for the RTS is based on the hypothesis that mild/moderate SUI results from compromise of periurethral supporting structures (Rehder and Gozzi, 2007). Through proximal placement of the mesh material, the dynamics of the bulbar urethra are modified to result in functional extension of the membranous and angulation of the bulbar urethra. The mechanisms for improved SUI with the ARS and quadratic sling are currently unknown and may result from a combination of urethral compression and angulation.

Implantation techniques for POP

Abdominal meshes (AM) (open and laparoscopic/robot)

The standard treatment of genital prolapse via the abdominal route is sacral hysteropexy or colpopexy, in which a mesh is attached to the anterior common vertebral ligament, in order to correct the anterior (cystocele) and apical (uterus or vaginal apex) and/or posterior (rectocele, enterocele) compartments. Either a prosthetic macroporous monofilament polypropylene mesh or a polyester mesh can be used. Various mesh fixation techniques have been described using non-absorbable sutures or anchor fixation/tacker/staplers. Following identification of the right ureter, the left iliac vein and the iliac vessel junction, the peritoneum above the sacral promontory, were incised medially to the right ureter and laterally to the sigmoid colon. The bladder is dissected from the upper half of the anterior vaginal wall. Concerning the apical compartment: (a) when the uterus is left in the pelvis, the anterior mesh is attached to the anterior part of the uterine isthmus (junction between the cervix and the anterior part of the uterine isthmus)and the mesh is passed laterally in the right broad ligament (or bilaterally); (b) when a concomitant hysterectomy is performed, a subtotal hysterectomy is usually done (in order to avoid an opening of the vagina) and the anterior mesh is attached to the conserved cervix; (c) in patients presenting with previous total hysterectomy, the mesh is attached directly to the vaginal wall. For the posterior mesh placement, a rectovaginal dissection is performed down to the level of the levator ani muscles and a mesh is placed and sutured to the levator ani muscles (or to the posterior vaginal wall) using a non-absorbable suture along the full length of the posterior vaginal wall. Two different promontory fixation techniques were available: prosthesis fixation to the promontory using a suture (non absorbable) or titanium tackers. A complete closure of the peritoneum is finally performed.

The risks associated with sacral colpopexy are the following: vaginal mesh exposure (2-5%), *de novo* constipation / obstructive defecatory syndrome (10%), per-operative bladder (1%) or bowel (0.1%) injury, *de novo* dyspareunia (1-3%), pelvic abscess (< 1%), spondilodiscitis (<0.1%) and visceral (bladder, rectum) mesh exposure (< 0.1%) (Maher *et al.*, 2013).

Sacral hysteropexy or colpopexy may be performed by laparotomy or by laparoscopy. Laparoscopic sacrocolpopexy is as efficient as open abdominal sacrocolpopexy, with a reduced rate of intraoperative bleeding hospitalisation and wound complications (Tyson

et al., 2013; Freeman *et al.*, 2013). Thus, the laparoscopic approach is recommended for sacral colpopexy. It is recommended not to use silicone-coated polyester, porcine dermis, fascia lata and polytetrafluoroethylene meshes.

The risk of vaginal mesh exposure is significantly increased in cases of sacrocolpopexy associated with concomitant total hysterectomy (8.6 %), in comparison to 2.2 % in those with previous hysterectomy (Costantini *et al.*, 2005, Zucchi *et al.*, 2010). Thus, if hysterectomy is required, it is recommended to perform a subtotal hysterectomy.

Even if the prevalence of complications/reintervention seems to be lower following sacral colpopexy when compared to vaginal meshes surgery (Maher *et al.*, 2011), serious complications have been described at short and long-term follow-up after sacral colpopexy (Nygaard *et al.*, 2913; Arsene *et al.*, 2014)

Robotic and laparoscopic sacral colpopexy had similar operative times, short-term anatomic cure rates, perioperative complications and length of hospital stay (Anger *et al.*, 2014). However, costs of robotic sacrocolpopexy are higher than laparoscopic. Thus, robotic sacral colpopexy is not recommended.

4.2.3. Results of treatment using meshes

Mesh surgery for SUI

- **Female patients**

Comparative data (RCT): MUS procedures vs other treatments

Stress urinary incontinence is a common, burdensome and costly condition for women with a negative impact on life quality. Non-surgical measures such as pelvic floor muscle training (PFMT) are useful treatment options in alleviating symptoms, although many women proceed with surgery, if these are not successful.

A recent RCT has shown that for women with moderate to severe SUI, an initial MUS procedure (without previous physiotherapy), as compared with initial physiotherapy, results in higher objective and subjective cure and global improvement rates at 12 months follow-up. So, women with moderate to severe SUI should be carefully counselled on these treatment options and their respective expected effectiveness (Labrie *et al.*, 2013)

MUS procedures vs Burch colposuspension and Marshall Marchetti Krantz

Several meta-analyses evaluated the efficacy, complications and reintervention rates of MUS compared to colposuspension (Schimpf *et al.*, 2014; Novara *et al.*, 2010; Ogah *et al.*, 2011) and have shown that MUS procedures were associated with comparable or significantly higher overall and objective cure rates when compared to Burch colposuspension and with shorter operative time and less postoperative *de novo* BOO or OAB (overactive bladder) symptoms, although they were associated with an increased risk of bladder injury.

Finally, RP MUS and TP MUS are associated with similar patient-reported cure of SUI at 12 months follow-up and MUS are associated with lower rates of de novo BOO and OAB symptoms.

MUS procedures vs 'traditional' suburethral slings (pubovaginal autologous fascia rectus slings)

Several meta-analyses showed that traditional slings have similar success rates as MUS procedures, but they are associated with longer operation duration and higher rates of adverse events (de novo BOO and OAB symptoms) (Schimpf *et al.*, 2014; Rehman *et al.*, 2011; Novara *et al.*, 2010; Ogah *et al.*, 2011).

Finally, MUS are associated with similar results when compared to 'traditional' slings, but with shorter operative duration and lower rates of adverse events (LE1), at 12-months follow-up.

Comparative data (RCT): MUS (RP, TO, SIS) vs MUS (RP, TO, SIS)

Comparative data (RCT) concerning MUS: RP vs TO

Several meta-analyses showed that RP MUS procedures are associated with higher objective cure rates when compared to TO MUS, but similar subjective cure rates (Schimpf *et al.*, 2014; Novara *et al.*, 2010; Ogah *et al.*, 2011). Furthermore, the RP approach is associated with an increased risk of bladder injury and haematoma and increased operation duration.

Finally, TO MUS and RP MUS are associated with similar patient-reported cure of SUI at 12 months follow-up (LE1). The RP approach is associated with higher rates of bladder injury (LE1) and TO approach is associated with higher rates of groin pain (LE1), at 12 months follow-up.

Comparative data (RCT) concerning RP MUS: bottom-to-top vs top-to-bottom

A meta-analysis showed that a RP bottom-to-top (= vagina to skin = bottom up) route is associated with higher cure rates and lower BOO symptoms and a decreased risk of bladder injury and blood loss when compared to RP top-to-bottom (skin to vagina = top down) (Schimpf *et al.*, 2014; Ogah *et al.*, 2011).

Finally, RP bottom-to-top (= vagina to skin = bottom up) approach is superior to RP top-to-bottom (skin to vagina = top down) (LE1).

Comparative data (RCT) concerning TO MUS: in-out vs out-in

Meta-analysis showed similar outcomes (cure rates and complications rates) for in-out TO technique and out-in TO technique (Schimpf *et al.*, 2014; Novara *et al.*, 2010).

Finally, TO in/out and TO out/in MUS are associated with similar patient-reported cure of SUI at 12 months follow-up (LE1).

Comparative data (RCT) concerning MUS: SIS/SIMS/SFSIS vs other MUS techniques

Main data concerned TVT-Secur procedure that has already been withdrawn from clinical use, since this technique was associated with lower cure rates when compared to standard (classical) MUS procedure (Schimpf *et al.*, 2014; Nambiar *et al.*, 2014).

A recent meta-analysis concluded that, excluding TVT-Secur, there was no evidence of significant differences in patient reported and objective and subjective cure rates between MUS and SIS at 18 months follow-up and SIS were associated with lower pain scores post-operatively (Mostafa *et al.*, 2014). Furthermore, a more recent well-conducted RCT also showed that, at short-term follow-up (12 months), Mini-Arc (a SIS/SIMS MUS) was not inferior with respect to cure and superior with respect to pain and recovery, when compared to Monarc (a standard TO out-in MUS) (Schellart *et al.*, 2014).

Finally, excluding TVT-Secur, SIS/SIMS/SFSIS and classical full length MUS are associated with similar patient-reported cure of SUI at 18 months follow-up (LE1) and SIS/SIMS/SFSIS are associated with lower post-operative pain scores.

Long-term outcomes are lacking concerning SIS/SIMS/SFSIS.

Patient stratification

Recurrence of SUI

Here, women who have previously undergone anti-incontinence surgery are discussed.

Most of RCT concerning colposuspension or MUS included naive patients (no previous anti-incontinence surgery) and women presenting with a recurrence of SUI.

No published RCT compared RP MUS and colposuspension in women presenting with recurrent SUI. Meta-analysis concluded that there was no evidence in objective and subjective symptoms between RP and TO MUS (LE 3) (Agur *et al.*, 2013).

Mixed urinary incontinence (MUI)

No RCT compared colposuspension, autologous slings and MUS in a mixed urinary incontinence population. Moreover, 'mixed urinary incontinence' definitions are very different between RCT. The proportion of women presenting with MUI in published RCT varied from 8 to 93% depending on the definition (Brubaker *et al.*, 2009).

Older women

There is little evidence that increasing age is an independent risk factor of failure or recurrence following MUS procedure (both for RP and TO approach) (Rechberger *et al.*, 2010; Barber *et al.*, 2008; Richter *et al.*, 2008; Groutz *et al.*, 2011) (LE3).

Although there is no consensus concerning the definition of an 'old' woman, a RCT was conducted in a group of 'old' women (> 70 years old) and showed that MUS RP procedure was associated with better quality of life and lower incontinence symptoms when compared to no treatment (LE2) (Campeau *et al.*, 2007).

No RCT compared colposuspension or autologous slings and MUS procedure in 'older' women.

Finally, there is no evidence that any surgical procedure is associated with better results in older women when compared to another procedure.

Adverse events

In a two-year follow-up study, which prospectively evaluated transobturator and retropubic mid urethral slings a total of 383 adverse events were observed among 253 of the 597 patients (42%). The safety committee considered that adverse events (20%) were considered serious and occurred in 70 women. Intraoperative bladder perforation (15 events) occurred exclusively in the retropubic group. Neurological adverse effects were more common in the tranobturator group than in retropubic (32 events vs 20 events respectively). 23 (4%) women experience mesh complications including delayed presentations in both groups. (Brubaker *et al.*, 2011)

Guidelines on surgical treatment for women with SUI

Guidelines from EAU (European Association of Urology), NICE / RCOG (United Kingdom), CNGOF (College National des Gynecologues et Obstétriciens Français) & AFU (Association Française d'Urologie) (France), ACOG (American College of Obstetricians and Gynecologist) and ACP (American College of Physicians) (USA) recommend first-line treatment with MUS (RP or TO) (grade: strong recommendation / Grade A; high quality evidence / LE 1) (Qaseem *et al.*, 2014; Fritel *et al.*, 2010; Smith *et al.*, 2013; Lucas *et al.*, 2013). Second line surgical therapies (open or laparoscopic colposuspension or autologous fascial slings) should be offered, if MUS cannot be considered (Grade C).

Conclusions

The amount of synthetic mesh used for the treatment of SUI is far less compared to the use of such mesh in POP repair.

There is robust evidence (LE1) to support the use of MUS from over 2,000 publications, making this treatment the most extensively reviewed and evaluated procedure for female SUI now in use. These scientific publications studied all types of patients, including those with co-morbidities such as prolapse, obesity and other types of bladder dysfunction. It is, however, acknowledged that any operation can cause complications. For MUS these include bleeding, damage to the bladder and bowel, voiding difficulty, tape exposure and pelvic pain; all of these may require repeated surgery, but this is uncommon. Nevertheless, the results of a large multi-centre trial have confirmed excellent and equivalent outcomes between a retropubic and a transobturator sling and a low rate of complications to be expected after treatment with MUS. (Richter *et al.*, 2010) Treatment success decreased over 5 years for retropubic and transobturator slings and did not meet the prespecified criteria for equivalence with retropubic demonstrating a slight benefit. However, satisfaction with both types of slings remained high. Women undergoing a transobturator sling procedure reported more sustained improvement in urinary symptoms and sexual function. New mesh erosions occurred in both types over time, although at a similar rate. (Kenton *et al.*, 2015). Additionally, long-term effectiveness of up to 80% has been demonstrated in studies including one that has followed up a small group of patients for 17 years (Nilsson *et al.*, 2013).

- **Male patients**

Review of surgery results

Clinical outcomes

Multiple series are currently available reporting outcomes of the various male sling techniques. However, given the nature of the studies performed and methodology for reporting, outcomes should be interpreted with caution. There is currently no accepted standard method for reporting pre- and postoperative degrees of incontinence or any consistent method for defining success with treatment. The majority of studies have poorly or undefined inclusion/exclusion criteria with significant heterogeneity of the patient population including inconsistent inclusion of patients with varied etiologies for SUI or prior radiation therapy. These factors, among others, limit the ability to draw comparisons between studies and techniques.

A comprehensive review on the results of male sling and AUS surgery was performed by Trost and Elliott (2012). As the bone anchor sling (BAS) has been available and utilised for a longer period of time than other slings, more studies are currently available for review with longer mean/median follow-up periods. For the purposes of that review, studies were included, if they were published within the past 10 years and examined synthetic sling placement only, as organic sling material is no longer commonly employed.

Overall results of the BAS demonstrated cure rates ranging from 37 to 67% with improvement noted in an additional 10–40%. The wide range of results is likely secondary to surgical method and the definitions for continence utilised and may also be due to a migration of case complexity. More recent reports have included an increased number of patients with prior radiation therapy and those with more severe preoperative incontinence. Several studies have noted significance in the association of preoperative continence and postoperative success rates with conflicting reports on the impact of radiation on overall success. Complications commonly reported include infection (2–15%), erosion (0–3%), de novo urgency/overactivity (0–14%), pain (0–73%) which typically resolves within 4 months and sling removal (0–13%) (Trost and Elliott, 2012).

Results from placement of the RTS have similarly demonstrated resolution or improvement in males with mild-to-moderate SUI in 9–62% and 16–46% of patients, respectively. With the notable exception of Cornel *et al.*, (2010), who reported a success rate of 9% and failure rate of 46% among 35 patients, other studies report higher cure rates of 52–74% with improvements noted in an additional 16–27%. Complications reported with the RTS include temporary urinary retention <2 weeks (0–24%), urethral injury (0–3%), pain (0–34%), need for sling removal (0–4%) and dysuria (0–14%).

It is notable that four studies examining RTS were prospectively designed, with three accruing over 110 patients (Rehder *et al.*, 2010; Cornel *et al.*, 2010; Cornu *et al.*, 2011; Bauer *et al.*, 2011). As with the BAS groups, improved outcomes were noted among patients with decreased preoperative incontinence, with a trend towards increased failures noted among patients with preoperative radiation therapy (Cornu *et al.*, 2011).

Two studies of interest investigated the role for RTS as a salvage technique in cases of recurrent incontinence following prior anti-incontinence surgery. Christine and Knoll (2010) reviewed 19 patients undergoing RTS in patients with recurrent incontinence

following prior AUS placement. Patients had self-reported pre-op pad usages of 2–5 ppd. Following RTS placement, 15/19 (79%) reported requiring 0 ppd (pads per day), with the remaining 4/19 (21%) describing improvement. Approximately half of the patients did not require reactivation of the sphincter. Similarly, Soljanik *et al.*, (2010) reported on 29 patients undergoing RTS following a previously failed sling procedure with preoperative mean pad requirement of 4.3 ppd. At 17 months follow-up, results demonstrated resolution of incontinence in 10/29 (35%) with improvement noted in an additional 16/29 (55%). These studies highlight the potential role for male sling placement as a potential adjunctive/salvage treatment; however, further validation is required prior to its consideration as a routine salvage measure.

A third category of currently available slings includes the ARS. Results of initial and longer-term follow-up demonstrate success rates of 13–100% with larger series reporting rates of 54–79%. Patients required adjustments in 10–100% of cases, many of which required repeated anaesthesia. Complication rates were significantly higher compared to other sling categories with infections (5–7%), erosion (3–13%), explantation (2–35%), bladder perforation (5–29%), retention (35%) and perineal pain (4–38%) most commonly reported (Trost and Elliott, 2012).

Adverse events

The adverse events of implanting a male sling are summarised in the following (Trost and Elliott, 2012):

Complications resulting from male sling implantation may be categorised as occurring intraoperative, early postoperative (<90 days) or late postoperative (>90 days). Intraoperative complications may include urethral injury occurring at the time of urethral dissection or passage of a trocar for male sling placement. If a small injury is recognised, placement of the male sling may continue at a separate site to prevent subsequent erosions. A large urethral injury should be repaired primarily with the procedure aborted and a catheter placed. Bladder injuries occurring during trocar passage may be managed with repassing of the trocar and subsequent catheterisation for a period of several days postoperatively. Given the relative incidence of bladder injury with retropubic sling placements, patients undergoing these procedures should undergo intraoperative cystoscopy to rule out bladder perforation.

Early postoperative complications include urinary retention, infection and/or erosion, perineal pain and *de novo* detrusor overactivity. Urinary retention typically occurs secondary to postoperative edema and resolves spontaneously in the majority of cases. Persistent retention lasting >8 weeks may indicate inappropriate sizing of the sphincter cuff, overtensioning of the sling, or sling malposition. Retention is typically managed with in-and-out catheterisation with suprapubic tube placement required in rare cases.

Infections of the sling material may be secondary to unrecognised urethral erosion versus intraoperative contamination. Preoperative patient factors including repeated device placements, prior erosions and radiation therapy all predispose patients towards a higher rate of postoperative infections. The most commonly isolated organisms with infection include S. aureus, S. epidermidis, Enterococcus, Methicillin resistant S. aureus and gram-negative bacilli (Magera and Elliott, 2008). Infections occurring beyond 90 days may be related to the hematogenous spread of bacteria at the time of additional procedures.

Urethral erosions occurring early in the postoperative period are likely secondary to unrecognised urethral injury occurring at the time of surgical implantation. Device erosions require explantation, even in the absence of infection, with possible repeat sling placement performed several months later pending sufficient recovery and absence of urethral stricture development.

Postoperative perineal pain is common with male sling placement, with some authors noting pain in 100% of male sling patients for periods up to 4 months. Patients may additionally develop *de novo* detrusor overactivity, which may be managed with anticholinergic therapy as indicated.

Patient stratification

According to Trost and Elliott (2012), deciding which procedure to perform in males presenting with stress urinary incontinence is based on several factors, which are discussed hereafter.

Most commonly, male slings are offered in cases of lower-volume incontinence (1–3 ppd), or in the setting of complicating patient factors including inability to function the AUS pump.

There is currently no universally accepted standard by which patients are stratified into receiving a male sling versus AUS. Similarly, there are no currently accepted objective measures by which men are formally evaluated for stress incontinence. Evaluating clinicians may elect to stratify patients based on subjective reporting of pad usage, objectively obtained 24-hour pad weights, or by the degree of SUI visualised on examination. This lack of consensus on the clinical evaluation of males with SUI is mirrored in the available published literature, which similarly lacks an accepted method of standard reporting.

Additionally, there are currently no publications that directly compare results for the various treatments of male SUI and as such, it is not possible to directly compare reported outcomes between studies. Based on the reported literature available, it is not possible to definitively identify one sling procedure as superior to another.

In general, available data on the various male slings have shown a reduction in overall efficacy in patients with pre-surgical, higher volume incontinence, and therefore AUS is typically chosen in these cases. Alternatively, male slings may be preferred in cases of diminished hand and/or cognitive ability, regardless of degree of incontinence as this may avoid potentially serious complications of urinary retention and its sequelae. Given the lack of data and guidelines, the decision as to whether to perform a male sling versus AUS depends on several factors including patient preference, surgeon comfort and experience with the available procedures and knowledge of the currently available outcomes and complications of each procedure.

Conclusions

Several therapies are currently available for the treatment of low-to-moderate volume incontinence including the AUS and several variations of male slings (BAS, RTS, ARS and quadratic sling). Patients with large-volume incontinence are best managed with AUS when found to be an appropriate surgical candidate. Complications of sling/AUS

placement include temporary retention, perineal pain, infections, erosions, *de novo* urinary symptoms and device malfunction.

Mesh surgery for POP

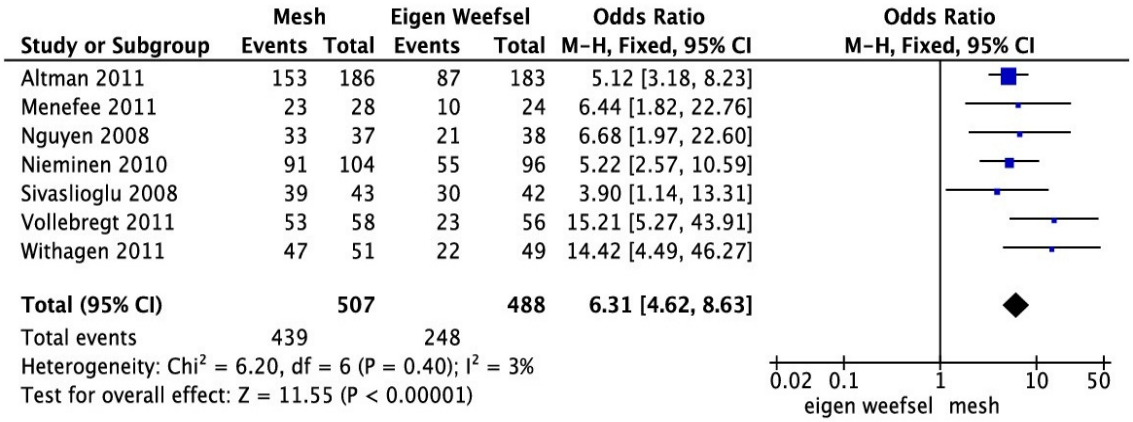
Results are presented regarding outcome including adverse results related to mesh placement (vaginal mesh exposure; bladder/rectal mesh exposure; mesh infection and mesh shrinkage = mesh contraction) and adverse effects which are not related to this procedure (dyspareunia; hispareunia; haematoma; bladder/rectal injury; abscess).

Comparative data (RCT): TVM implantation vs. vaginal POP surgery using native tissues

Recently a (Dutch) review (Milani *et al.*, 2013) was published on 10 randomised controlled trials comparing outcomes of synthetic mesh to native tissue surgery for the vaginal repair of POP. Anatomical and functional outcomes were reported as well as postoperative and de novo dyspareunia. These data demonstrated superior anatomic outcomes (POP stage <II) for the anterior vaginal compartment and could not demonstrate a significant difference in de novo or postoperative dyspareunia, comparing synthetic mesh implantation and POP repair using native tissues (see Figures 2-4).

Figure 2 shows the results of a meta-analysis of randomised controlled trials that compare strict anatomic outcomes (POP-Q stage <II) for the anterior vaginal compartment between mesh implantation and the use of native tissue. The Odds ratio for anatomic success in the anterior compartment was 6.31 (95% CI 4.62-8.63)

Figure 2: Anatomic success (POP stage < II) in the anterior vaginal compartment



Figures 3 and 4 show the results of meta-analysis of randomised controlled trials that compare postoperative and de novo dyspareunia between mesh implantation and native tissue repair at 12 months follow-up. No significant difference in postoperative dyspareunia (total of 295 patients) or de novo dyspareunia could be demonstrated.

Figure 3: Postoperative dyspareunia

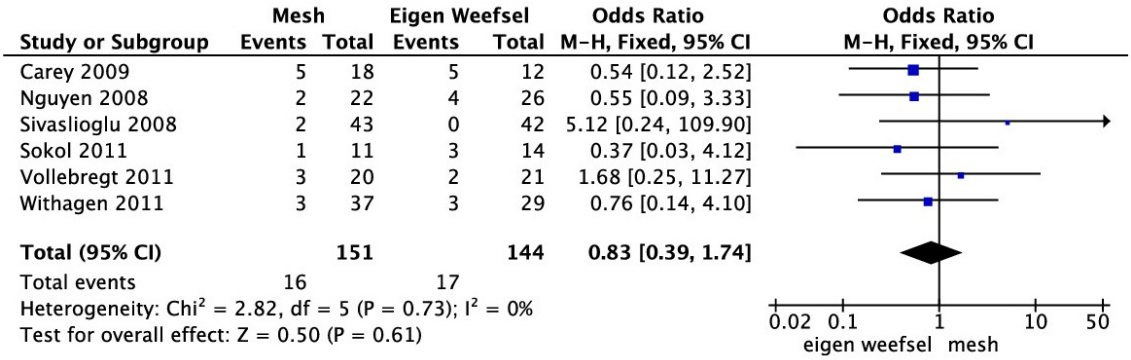
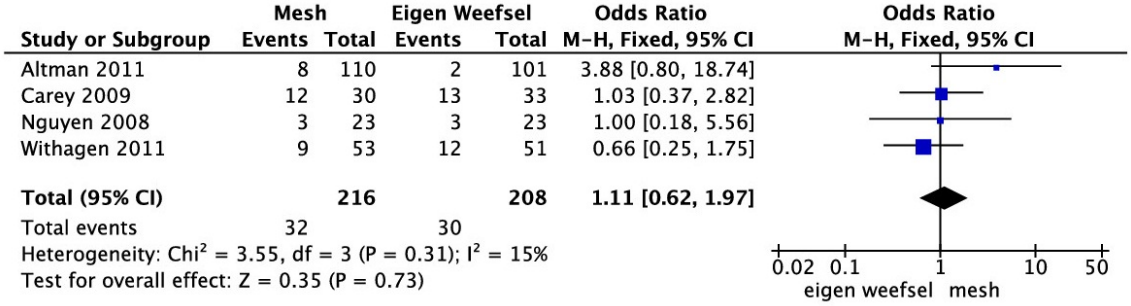


Figure 4: De novo dyspareunia



The optimal surgical repair of POP is not yet known. Recently, the International Urogynecological organisations (IUGA and ICS) emphasised the importance of the use of clinically relevant outcome measures. From a patient perspective, the subjective outcome measures, that is, the elimination of bothersome symptoms, prevail above objective (anatomical) outcomes (Toozs-Hobson *et al.*, 2012). Hereunder, (Tables 1-3) the results of a recent systematic review and meta-analysis are shown for the comparison of these various clinically relevant outcomes between the use of native tissues or synthetic mesh implantation for the repair of pelvic organ prolapse. Table 1 shows the results for the repair of the anterior vaginal compartment, Table 2 for the posterior vaginal compartment and Table 3 shows results of cases where more than one vaginal compartment was involved in the repair (Dutch Guideline, 2014).

From left to right columns in the following table, the outcome measure is defined, the cases and denominator are shown, and the calculated relative risk with 95% confidence intervals and the interpretation is given.

1

2 *Table 1: Anterior colporrhaphy (native tissue repair) versus mesh implantation (TVM) for*
3 *the surgical repair of anterior compartment prolapse.*

Outcome measure	Surgery n/N		RR (95% CI)	*Conclusion*
	AC	TVM		
Number of women with recurrent prolapse symptoms (bulge)	90/271 98/349	53/284 62/363	1.77 (1.32-2.37) 1.64 (1.24-2.16)	*Subjective recurrence higher in case of use of native tissue*
Satisfaction of patients (PGI-I)				*No research available*
Quality of life after operation (P-QOL of PFDI-20) mean/N	7.5/42 45/37	6.2/43 34/37	MD 0.22 (-0.21, 0.65) MD 11.0 (-3.36, 25.36)	*No difference*
Number of women with anatomical prolapse recurrence regardless which compartment	6/20	1/20	6.00 (0.79-45.42)	*No difference*
Number of women with an anatomical recurrence of the anterior vaginal compartment	200/410 220/478 149/272 51/138 147/296 281/719	59/424 69/498 43/277 16/147 43/302 99/736	3.39 (2.62-4.38) 3.23 (2.55-4.10) 3.83 (2.34-6.26) 3.41 (2.05-5.68) 3.59 (2.38-5.40) 2.82 (2.19-3.62)	*Objective recurrence higher in case of use of native tissue*
Number of women with de novo prolapse of the middle vaginal compartment				*No research available*
Number of women with *de novo* prolapse of the posterior vaginal compartment	2/15	13/26	OR: 0.15 (0.03-0.82)	*Less de novo prolapse when using native tissue*
Number of women with re-operation for prolapse	14/459	6/471	2.18 (0.93-5.10)	*No difference*
Number of women with *de novo* dyspareunia	9/213	15/216	0.61 (0.28-1.32)	*No difference*
Sexual functioning score (PISQ-12) mean/N	35.1/189 33/37 226	35/200 37/34 237	MD 0.10 (-0.17, 0.37) MD -1.00 (-3.16, 1.16) MD 0.08 (-0.18, 0.35)	*No difference*

Outcome measure	Surgery n/N		RR (95% CI)	*Conclusion*
Number of women with	3/324	41/320	0.58 (0.36-0.94)	*Less de novo SUI using native tissue*
de novo stress incontinence	27/344	42/340	0.62 (0.40-0.98)	
Number of women with de novo urgency, detrusor over activity or over active bladder				*No research available*
Number of women with subsequent urinary incontinence surgery	15/368	12/380	1.29 (0.63-2.63)	*No difference*
Number of women with mesh exposure	0/547	64/563	0.07 (0.03-0.18)	*Native tissue protects against mesh exposure*
Number of women requiring surgery because of mesh exposure	0/460	31/471	0.09 (0.03-0.29)	*Native tissue protects against mesh exposure*
Number of women with post-operative complications				*No research available*
Costs				*No research available*
MD = mean difference; OR = odds ratio; RR = Relative Risk; TVM = transvaginal mesh; AC = anterior colporrhaphy				

1

2 *Table 2: Posterior colporrhaphy (native tissue repair) versus mesh implantation (TVM)*
3 *for the surgical repair of posterior compartment prolapse.*

Outcome measure	Surgery n/N		RR (95% CI)	*Conclusion*
	PC	TVM		
Number of women with recurrent POP symptoms (bulge)	7/24	6/26	1.26 (0.49-3.23)[1]	*No difference*
Satisfaction of patients (PGI-I) – much better	15/22	17/28	0.99 (0.64-1.53)[1]	*No difference*
Quality of life after operation (P-QOL of PFDI-20) mean/N				*Not published separately*
Number of women with anatomical recurrent prolapse regardless of which compartment	14/25	18/30	0.93 (0.59-1.47)[1]	*No difference*

Outcome measure	Surgery n/N		RR (95% CI)	*Conclusion*
Number of women de novo prolapse of the anterior vaginal compartment	4/24	16/30	0.31 (0.12-0.81)[1]	*Significantly less when treated with native tissue*
Number of women with de novo prolapse of the middle vaginal compartment	0/24	0/30		*No difference*
Number of women with anatomical recurrence of the posterior vaginal	9/25	1/30	10.80 (1.47-79.53)[1]	*Significantly more after using native tissue*
Number of women requiring a subsequent operation for prolapse				*Not reported*
Number of women with *de novo* dyspareunia				*Not separately reported*
Sexual function score (PISQ-12)				*Not reported*
Number of women with *de novo* stress incontinence	1/25	2/28	0.56 (0.05-5.81)[1]	*No difference*
Number of women with *de novo* urgency, detrusor over activity or over active bladder				*Not reported*
Number of women with subsequent incontinence surgery				*No difference*
Number of women with mesh exposure	0/25	5/32	[1]	*No exposure after use of native tissue*
Number of women with surgery because of mesh exposure				*No exposure after use of native tissue*
Number of women with post-operative complications				*Not reported*
Costs				*No research available*

PC =posterior colporrhaphy; RR = Relative Risk; TVM = transvaginal mesh;

1 only one study: Withagen *et al.*,2011

Table 3: Vaginal surgical repair of multiple compartments using native tissues versus mesh implantation.

Result	Surgery n/N		RR (95% CI)	*Conclusion*
	AC+PC	TVM		
Number of women with recurrent prolapse symptoms (bulge)	29/173	24/167	1.17 (0.71-1.92)	*Subjective recurrence higher using native tissue*
Satisfaction of patients (PGI-I) – much better	85/121	76/114	1.03 (0.87-1.23)	*No difference*
Quality of life after operation (P-QOL or PFDI-20) mean/N				*No difference*
Number of women with recurrent anatomical prolapse regardless of which vaginal compartment	123/249	85/256	1.49 (1.20-1.84)	*Objective recurrence higher using native tissue*
Number of women with *de novo* prolapse of the anterior vaginal compartment	7/33	16/30	0.40 (0.19-0.83)	*Significantly lower using native tissue*
Number of women with *de novo* prolapse of the middle vaginal compartment	0/39	2/56	0.28 (0.01-5.78)	*No difference*
Number of women with anatomical recurrence of the posterior vaginal compartment	3/26	13/32	0.28 (0.09-0.89)	*Significantly lower using native tissue*
Number of women who are operated for prolapse	7/189	4/194	1.62 (0.54-4.85)	*No difference*
Number of women with *de novo* dyspareunia	19/103	14/110	1.45 (0.77-2.74)	*No difference*
Sexual function score (PISQ-12) mean/N	33-35/61	34 / 64	0.72 (-1.41–2.86)	*No difference*
Number of women with *de novo* stress incontinence	27/144	37/142	0.72 (0.46-1.12)	*No difference*
Number of women with *de novo* urgency, detrusor over activity or over active bladder				*Not investigated*
Number of women with mesh exposure	0/249	39/256	0.01 (0.00-0.21)	*Mesh increases risk for exposure*

Result	Surgery n/N		RR (95% CI)	*Conclusion*
Number of women needing a surgery because of mesh exposure	0/189	18/194	0.08 (0.02-0.42)	*Mesh is risk full for exposure*
Number of women with post-operative complications				*No research available*
Costs				*No research available*

AC = anterior colporrhaphy, PC = posterior colporrhaphy; RR = Relative Risk; TVM = transvaginal mesh

Conclusion

For the anterior vaginal compartment, there is convincing evidence that the use of a synthetic mesh to repair a prolapsed anterior vaginal wall is subjectively and objectively superior to a native tissue repair. There is, however, no difference in health related quality of life between mesh and native tissue repair. The rate of de novo POP of the untreated vaginal compartment is significantly higher when synthetic mesh is used. There is no evidence for a difference in the need for subsequent operations for POP or the occurrence of *de novo* dyspareunia or sexual function. The use of mesh results in higher rates of reported SUI, although this was not reflected in a higher rate for SUI surgery. Mesh exposure is reported frequently.

For the posterior vaginal compartment, there is moderate evidence that the use of mesh results in higher rates of objective cure and *de novo* POP of the anterior vaginal compartment, but no differences in subjective cure or de novo SUI. Mesh exposures are reported frequently.

For the treatment of more than one vaginal compartment, the meta-analysis showed that the use of mesh resulted in higher rates of subjective and objective 'cure', but also in significantly higher rates of de novo POP of the untreated vaginal compartments. There were no differences in patient satisfaction; health related quality of life, subsequent operations for POP, *de novo* dyspareunia, sexual function scores or *de novo* SUI. Mesh exposures, however, were frequently reported.

The follow-ups of selected papers for that meta-analysis were mainly short (12 months) and sometimes medium-term (36 months). Long-term results (5-10 years) of RCT's are not yet published and, thus, are yet unavailable for analysis.

Adverse events

- Mesh exposure

Mesh exposure is the condition whereby synthetic mesh is displayed/exposed (usually visualised through separated vaginal epithelium) (Haylen *et al.*, 2012) and is the most frequently reported complication with rates ranging from 4-19%. These exposures can cause pain during sexual intercourse, cause blood loss or foul vaginal discharge, but can also be asymptomatic. The risk of exposure increases with tobacco use (OR 3.1; 95% CI

1.1-8.7), decreased clinical experience of the surgeon (OR: 2.0; 95% CI 1.2-3.4) and with the use of a 'total' (that is anterior and posterior) mesh (OR: 3.0; 95% CI 1.2-7.0) (Withagen *et al.,* 2011).

- Dyspareunia

Pain during sexual intercourse is frequently reported by women suffering from pelvic organ prolapse and usually diminishes after surgical repair of the prolapsed vaginal compartments. In a systematic review of 54 studies on 4566 patients, dyspareunia rate after a vaginal mesh procedure was reported to be 8.9% (range; 0-67%; 95% CI 8.0-10.0)(Abed *et al.,* 2011). Randomised trials comparing vaginal mesh versus native tissue repair surgery however did not demonstrate a difference in *de novo* dyspareunia, nor in postoperative dyspareunia (Milani *et al.,* 2013; Dietz and Maher 2013). The most important risk factor for postoperative dyspareunia was pre-operative dyspareunia. (Withagen *et al.,* 2011).

- Pain

Pain is a complication that can occur after any surgical repair of vaginal prolapse. Pain caused by shrinkage of vaginal tissue caused by an excessive inflammatory reaction against the polypropylene mesh, which acts as a foreign body is of a different nature and can be serious and difficult to treat. Pain in the lower abdomen or pubic region 12 months after a mesh augmented prolapse repair is reported by between 3-10% of the patients. Randomised studies however could not demonstrate a difference between a mesh augmented and a conventional native tissue repair of pelvic organ prolapse. (Milani *et al.,* 2013; Withagen *et al.,* 2011)

- Other complications

Other complications that can occur after vaginal mesh surgery are haemorrhage, bowel and or rectal injury, urinary infection and postoperative retention. These complications also occur after native tissue surgery.

Guidelines on surgical treatment for women with POP

The objective of this paragraph is to describe main recommendations concerning POP surgery in Europe and USA. The reported recommendations have been elaborated by international (IUGA, EAU) or national scientific societies in UK, Netherlands and France.

List of existing recommendations:

- IUGA roundtable (2011): Davila *et al.,* 2012; Slack *et al.,* 2012; Winters *et al.,* 2012; Miller *et al.,* 2012.

- Dutch guidelines on mesh surgery in POP surgery and MUS (2012, updated in 2014).

- French guidelines on mesh placement in POP surgery (2011 and 2013).

- The UK's National Institute for Health and Clinical Excellence (NICE) has issued full guidance to the NHS in England, Wales, Scotland and Northern Ireland on infracoccygeal sacropexy using mesh for uterine prolapse repair.

- NICE was notified of various procedures for the treatment of pelvic organ prolapse. NICE asked the Review Body for Interventional Procedures to undertake a systematic

review of these procedures. The Interventional Procedures Advisory Committee (IPAC) considered the systematic review and has also produced guidance on: infracoccygeal sacropexy using mesh for vaginal vault prolapse repair, sacrocolpopexy using mesh for vaginal vault prolapse repair, sacrocolpopexy using mesh for uterine prolapse repair and insertion of uterine suspension sling (including sacrohysteropexy) using mesh for uterine prolapse repair.

- Uterine prolapse occurs when the womb (uterus) slips down from its normal position into the vagina. Infracoccygeal sacropexy is an operation that involves the insertion of a piece of material (mesh) with the aim of holding the womb in place.

- Risks and possible problems: Mesh erosion requiring further treatment occurred in 4 out of 35 women who had infracoccygeal sacropexy alone and in 6 out of 44 women who had the procedure done together with a hysterectomy. As well as looking at this study, NICE also asked expert advisers for their views. These advisers are clinical specialists in this field of medicine. The advisers said that problems may include mesh erosion, infections, damage to the bladder, bowel or rectum and painful sexual intercourse. The advisers also said that there may be fewer complications with newer types of mesh. For more information about prolapse of the womb, a good place to find out more may be NHS Choices (www.nhs.uk). Your local patient advice and liaison service (usually known as PALS) may also be able to give you further information and support.

Mesh surgery for CFD

It has already been mentioned above that CFD do not fall exactly within the scope of this Opinion and are only mentioned here because the Dutch Health Inspectorate reported a considerable number of patients with complaints that had undergone a ventral rectopexy for rectal prolapse (Dutch Health Care Inspectorate, 2013).

4.2.4. Learning curve and clinical experience

Mid-urethral sling surgery

The surgical duration of TVT surgery is shortened after the operator had performed 15 operations (LE 4) (Ito *et al.*, 2011).

Higher rates of complications mainly occur in the first 4 months of training (LE 4) (Maguire *et al.*, 2013).

During the learning phase (50 first MUS procedures), the complications rates (bladder injuries, urinary retention and *de novo* bladder outlet obstruction symptoms) are higher (Lebret *et al.*, 2001).

Concerning the effect of a learning curve on the success rates (objective and/or subjective cure rates), the published data remain controversial. Cetinel *et al.*,(2004) observed comparable outcomes (subjective cure rates) 2 years after MUS procedure, irrespectively to surgeon 'experience' (< 20 MUS procedures vs > 20 MUS procedures). Koops *et al*, (2006) reported that, at 2 years follow-up, the outcomes (objective and subjective cure rates) observed following 20 MUS procedures are better than those

observed during the 10 first procedures (LE 4). However, at 5 years follow-up, another study observed that subjective cure rates were not related to surgical volume of the surgeon who performed the procedures (< 50 procedures vs > 50 procedures) (LE 4) (Holmgren *et al.*, 2005).

Finally, the learning curve for MUS surgery is probably variable (from one trainee to another) and may be longer than expected (learning curves should be individualised). Numerous confounding variables exist, such as trainee's prior experience, the difficulty of procedures and the level/quality of the supervision by a 'senior surgeon' (Khan *et al.*, 2014).

Pelvic organ prolapse surgery with meshes

o Laparoscopic sacral colpopexy

A. Laparoscopic sacral colpopexy (LSC) requires the attaining of laparoscopic suturing and knot tying skills. Claerhout *et al.*, (2009) observed that LSC operative duration decreased rapidly during the first 30 procedures and reached steady state after 90 cases. However, complication rates remained unchanged throughout this learning curve series. Using a cumulative sum approach, they hypothesised that adequate learning occurred after 60 cases (LE 4) (Claerhout, 2009). Akladios *et al.*, (2010) also observed that LSC operation duration decreased after 25 procedures. The complication rates were also low throughout this series and were not affected by learning curve. However, this study analysed the learning curve of a senior urogynecologic surgeon who was initiated into this technique, and not the learning curve of a trainee.

Kantartzis *et al.*, (2013) analysed the learning curves of the first 180 LSC done by 4 attending urogynecologists and observed that there was no significant difference in the rate of overall complications regardless of the number of prior procedures performed (LE 4).

Mustafa *et al.*, (2012) observed that LSC operative time decreased considerably following the first 15 cases (LE 4).

However, since complication rates associated with LSC are low, the published series cannot assess the effect of under-experience since the number of cases is few in each series. Furthermore, the complication rates are probably limited because of the supervision by a 'senior surgeon' during this learning curve.

Prior training in laparoscopic suturing coincided with a short learning process for the phases requiring suturing (Claerhout *et al.*, 2014). The most time-consuming step is the dissection of the vault, for which it took the trainee 31 procedures to achieve an operation time comparable to that of the teacher (Claerhout *et al.*, 2014).

Learning curve for robot-assisted sacrocolpopexy (RASC) may be shorter than learning curve for LSC but there is no precise data concerning this point (Serati *et al.*, 2014).

o Mesh placed by vaginal route

Bafghi *et al.*, (2009) observed that operation duration decreased and then remained stable after 18 procedures.

Concerning the prevalence of vaginal mesh exposure, Guillibert *et al.*, (2009) observed that women treated by vaginal estrogens and those operated by the most experienced surgeon had less exposure. However, following multivariate analysis, the only independent risk factors of exposure were the kind of prosthesis, age under 60 and concomitant hysterectomy (Guillibert *et al.*, 2009).

Achtari *et al.*, (2005) showed that the prevalence of mesh exposure was associated with surgeon experience.

Withagen *et al.*, (2011) demonstrated that every decade of clinical experience reduced the risk for mesh exposure in transvaginal mesh surgery by 50%: clinical and surgical experience was inversely related to the risk of exposure (OR 0.5, 95% CI 0.3– 0.8 per decade).

Impact of treatment centre and medical specialty

Concerning mesh use in POP surgery, Rogo-Gupta *et al.*, (2012) showed that intermediate-volume (OR 1.53; 95% CI 1.44-1.62) and high-volume (OR 2.74; 95% CI 2.58-2.92) surgeons are more likely to use mesh than low-volume surgeons. Compared with women who underwent operations performed by gynecologists, those treated by urologists are more than three times more likely to undergo mesh-augmented prolapse repair (OR 3.36; 95% CI 3.09-3.66).

Conclusion

There is a learning curve for MUS procedures and for POP surgery procedures, especially concerning operation duration, and the evidence would suggest only experienced surgeons (such as > 20 cases performed under supervision of an experienced surgeon) should perform this kind of surgery unsupervised.

4.2.5. Mitigating risks through patient selection and counselling

Patient selection

In the case of urogynaecological mesh devices, there is at present very little robust evidence available to inform patient selection when used either for pelvic organ relapse or stress urinary incontinence.

When considering surgery for SUI in female patients the evidence (**Error! Reference source not found.**5) stated in the 2014 guidelines of the EAU (EAU, 2014) should be taken into account.

Ideally the increasing literature on complications (and by deduction on successful outcomes for patients) will in the future support a meta-analysis of patient selection for avoiding poor outcomes.

Evidence summary	LE
Compared to colposuspension, the retropubic insertion of a mid-urethral synthetic sling gives equivalent patient-reported cure of SUI at 12 months.	1a
Compared to colposuspension, the transobturator insertion of a mid-urethral synthetic sling gives equivalent patient-reported outcome at 12 months.	2
Mid-urethral synthetic sling inserted by either the transobturator or retropubic route gives equivalent patient-reported outcome at 12 months.	1a
The skin-to-vagina (top down) direction of retropubic insertion of mid-urethral sling is less effective than a vagina-to-skin (bottom up) direction.	1a
Mid-urethral sling insertion is associated with a lower rate of a new symptom of urgency, and voiding dysfunction, compared to colposuspension.	1a
The retropubic route of insertion is associated with a higher intra-operative risk of bladder perforation and a higher rate of voiding dysfunction than the transobturator route.	1a
The transobturator route of insertion is associated with a higher risk of chronic pain at 12 months than the retropubic route.	1a
The skin-to-vagina direction of both retropubic and transobturator insertion is associated with a higher risk of postoperative voiding dysfunction.	1b
Older women benefit from surgical treatment for UI.	1
The risk of failure from surgical repair of SUI, or suffering adverse events, appears to increase with age.	2
There is no evidence that any surgical procedure has greater efficacy or safety in older women than another procedure.	4
In women undergoing surgery for SUI, coital incontinence is likely to improve.	3
Overall, sexual function is unlikely to deteriorate following SUI surgery.	3
There is no consistent evidence that the risk of postoperative sexual dysfunction differs between mid-urethral sling procedures.	3

Figure 2: Evidence summary to be considered when selecting female patients with SUI for surgery.

Men can also develop SUI following prostatic surgery and have been treated with synthetic slings. The evidence summary of the 2014 EAU guidelines (EAU, 2014) in this case is shown in Figure 6.

Evidence summary	LE
There is limited short-term evidence that fixed male slings cure or improve post-prostatectomy incontinence in patients with mild-to-moderate incontinence.	3
Men with severe incontinence, previous radiotherapy or urethral stricture surgery may have less benefit from fixed male slings.	3
There is no evidence that one type of male sling is better than another.	3

Figure 3: Evidence summary to be considered when selecting male patients with SUI for surgery.

A useful consensus statement published in the International Urogynaecology Journal (Davila *et al.*, 2012) relates to the management of pelvic organ prolapse. This highlights the following patients groups for which caution should be exercised regarding transvaginal mesh implants:

- Primary prolapse cases.
- Patients younger than 50.

- Lesser grades of prolapse (POP-Q ordinal grade 2 or less). Patients with mild to moderate (pelvic organ prolapse quantification; asymptomatic prolapse do not necessarily require surgical management. The decision to operate should be based upon symptomatic problems from the prolapse defined by the patient[2]
- Posterior compartment prolapse without significant apical descent.
- Patients with chronic pelvic pain.
- Postmenopausal patients who are unable to use vaginal oestrogen therapy since this will be first line therapy for erosion.

However, other factors may also increase the likelihood of complications associated with urogynaecological mesh implantation. These include:

- Surgeon's lack of clinical and surgical experience (Withagen *et al.*, 2011)
- Patient factors including:
    - Lower BMI (Sirls *et al.*, 2013)
    - Increased BMI
    - Increased Age (Kokanali *et al.*, 2014)
    - Previous surgical history, especially previous vaginal surgery for POP or SUI
    - Comorbidities which are risk factors for impaired tissue healing, such as diabetes mellitus, smoking and steroid use
    - Concurrent procedures including vaginal hysterectomy (Araco *et al.*, 2009; Akyol *et al.*, 2014)
    - Grade of prolapse.

4.2.6. Patient counselling

The informed consent process should be a wide-ranging discussion with the patient regarding her specific situation. This discussion should cover issues such as:

- The patient should be informed that limited robust data is available on the efficacy and safety of many of the transvaginal mesh products available for POP and that particularly long-term follow-up is currently not available which makes a balanced estimate of the risk/benefit ratio difficult. There is considerably more robust evidence on the safety and efficacy of polypropylene mesh use for SUI (RANZOG, 2013; Nillsson *et al.*, 2013)
- Potential benefits and complications of prolapse surgery in general versus the status quo or using conservative treatments (e.g., pelvic floor exercises or vaginal pessary).

- Potential benefits and complications of transvaginal mesh specifically when considered appropriate (Table 1 - Table 3).

- Alternatives to surgical management, including non-surgical options such as pelvic floor muscle training (Hagen *et al.*, 2014) and vaginal support pessaries.

- Other alternative surgical treatments such as conventional native tissue repair, as well as abdominal sacrocolpopexy (open or laparoscopic) in appropriate and certain anatomical and functional circumstances. Sacrocolpopexy is not a general alternative for vaginal mesh implantation. It depends on the anatomic and functional indications and has its own risk/benefit ratio, which in some instances can be more serious and needs to be outweighed in the shared decision process with the patient.

- Complications discussed of transvaginal mesh including mesh exposure/ erosion, vaginal scarring/stricture, fistula formation, dyspareunia, urinary problems, infection, perforation and/or pelvic pain, which may require additional intervention and may not be completely resolved even with mesh removal.

- Pain and or dyspareunia caused by prolapse surgery with or without mesh should be discussed based on the available scientific evidence and not on authority-based Opinions.

- Provision of written documentation, including device labelling when available.

If mesh procedure is considered, patients should be informed of the following additional issues (Health Canada, 2014):

- Through what route the mesh will be placed (abdominal, transvaginal, transperineal).

- That a mesh is considered a permanent implant; removal of mesh or correction of mesh-related complications may involve subsequent surgeries.

- That complete removal of mesh may not be possible and additional surgeries may not fully correct some complications.

- Patients should be encouraged to ask their doctor questions on why he/she thinks that mesh implantation is particularly beneficial for her and what the evidence or level of experience of the doctor is who is supposed to perform the procedure as well as what particular risks are involved in the proposed procedure.

4.2.7. Risk assessment and recommendations by National Associations

In 2007 and 2009 (December), the French National Authority for Health (Haute Autorité de Santé (HAS)) published information for the public and health professionals, concerning the assessment of meshes used for the treatment of SUI or POP. Eventually: 1) the use of polypropylene slings for SUI surgery was approved; 2) the use of polypropylene or polyester meshes for POP surgery by abdominal route was also approved; only macroporous meshes with pore size > 10mm and low grammage of <

150 g/m^2 should be used); 3) the use of polypropylene meshes for POP surgery by vaginal route was not recommended; (lack of conclusive data concerning side effects and actual efficacy compared to autologous techniques).

In the USA in October 2008, the US Food and Drug Administration (FDA) issued a Public Health Notification (FDA, 2008) regarding vaginal mesh providing advice for surgeon training and informed consent for patients. Serious complications requiring further surgery were described as "rare". However, from 2008 to 2010 there was a fivefold increase in adverse event reports to the FDA in relation to the use of vaginal mesh to treat pelvic organ prolapse. In response to the rise in reporting, and following an FDA internal review, including a systematic literature review, a second Safety Update was issued in July 2011 (FDA, 2011). This update states that: 1) "serious adverse events are NOT rare, contrary to what was stated in the 2008 PHN"; and 2) "transvaginally placed mesh in POP repair does NOT conclusively improve clinical outcomes over traditional non-mesh repair". The update made a distinction between the risks associated with abdominal implantation of surgical mesh for pelvic floor repair and vaginal implantation, concluding also that: "There does appear to be an anatomic benefit to anterior repair with mesh augmentation. This anatomic benefit may not result in superior symptomatic outcomes or lower rates of repeat surgery for recurrent prolapse compared to traditional POP repair without mesh".

FDA committee consultation and further regulatory action were announced by the 2011 publication, and since then the FDA has increased the required post market surveillance of these devices. Manufacturers of urogynaecological mesh devices have also been required to undertake mandatory post market studies to provide comparative data between mesh kits and conventional surgery. In April 2014, the FDA issued two proposals to address the risks associated with surgical mesh for transvaginal repair of pelvic organ prolapse. If finalised, the orders would reclassify surgical mesh for transvaginal POP according to FDA's scheme from a moderate-risk device (class II) to a high-risk device (class III) and require manufacturers to submit a premarket approval (PMA) application for the agency to evaluate safety and effectiveness.

As noted by the RANZCOG publication, the FDA conclusions have sparked further debate within the medical and patient community. In response to these publications and regulatory changes use of urogynaecological mesh in the USA has declined by 40–60% (Daly *et al.*, 2014). In addition, a number of manufacturers have withdrawn their meshes from the USA market.

Health Canada has issued a Health Advisory on 4 February 2010 (Health Canada, 2010), which was revised on March 2013. (Health Canada, 2013, Appendix O) This advisory provides a general statement regarding the potential risks associated with the use of surgical mesh in the repair of POP/SUI. The Advisory notes the increased Canadian and international reports of surgical complications associated with urogynaecological mesh use and requests the reporting of any adverse event associated with this type of device.

On May 2014, Health Canada released two health notices (Health Canada, 2014). The first was a safety information update to hospitals containing recommendations for surgical mesh for POP procedures and SUI procedures. These recommendations included statements regarding the potential for higher rates of complications in transvaginal placement of mesh compared to abdominally placed mesh or native tissue repair. Other recommendations discussed the importance of surgeon training. A second information

notice was released informing patients of the potential risk of complications associated with transvaginal implantation of surgical mesh devices for the treatment of POP and SUI. The latest statement includes the following comment "The use of transvaginal mesh devices for POP and SUI repair has been associated with reports of acute or chronic pain, pain during sexual intercourse, mesh erosion and shrinkage, infection, urinary problems, organ or blood vessel perforation, nerve damage, bleeding, vaginal tightness and/or shortening, and recurrent POP and SUI. Additional surgery may be required and may not fully correct some complications. Health Canada is reviewing labelling related to these products to determine if it provides appropriate safety information. Additional safety information in the labelling will be requested, as needed."

In Australia, from 2008 the Therapeutic Goods Administration (TGA) has been closely monitoring urogynaecological meshes and has continued to publish information for the public and health professionals. A review of urogynaecological meshes was undertaken by TGA in 2010. Following this review, a detailed analysis was undertaken in 2013 of the available published literature, the information supplied with each device and associated training materials provided by sponsors and manufacturers. The Urogynaecological Devices Working Group (established under the Advisory Committee on the Safety of Medical Devices) provided expert advice to the TGA on this review.

As part of the review, the TGA undertook a literature search of materials published since 2009. The overall quality of the literature was found to be poor. As a consequence, there was an absence of evidence to support the overall effectiveness of these surgical meshes as a class of products. However, the literature did identify the already known adverse outcomes associated with their use.

The TGA review identified inadequate training/experience for surgeons doing the implantations as a factor in increasing the risk of complications. Certain patients, including those who smoked or were obese, were found to be at higher risk of adverse events and repeated procedures.

As a result of that review, which has raised a number of concerns, the TGA is currently reassessing the clinical evidence for each individual mesh implant to determine if they comply with the Essential Principles, which set out the requirements for safety and performance necessary for inclusion on the Australian Register of Therapeutic Goods (ARTG).

Where individual meshes are found to be noncompliant, regulatory action, such as cancellation or suspension of particular devices from the Australian Register of Therapeutic Goods (ARTG), will be pursued.

5. OPINION

5.1. Terms of reference

5.1.1. Risks associated with the use of mesh in urogenital surgery

Are specific meshes, in terms of designs and/or materials, considered to be of a higher risk? If possible list and describe the risks. (Q1)

There are a number of different types of meshes, which include:

- Allografts (e.g., cadaveric fascia, dura mater)
- Xenografts (e.g., porcine, bovine)
- Autografts (e.g., fascia lata, rectus fascia)
- Synthetic meshes (non-absorbable, e.g., polypropylene mesh)

In this Opinion, the SCENIHR considers the uses of synthetic non-absorbable meshes.

Current consensus is that Type 2 (microporous, less than 10 microns, mono and multifilament) and 4 (sub-micronic and monofilament) are not appropriate for use in this clinical context.

Current evidence suggests:

- Type 1 polypropylene macroporous monofilament is considered to be the most appropriate synthetic mesh for vaginal use.
- Type 1 polypropylene macroporous monofilament and type 3 microporous, multifilament polyester are considered to be the most appropriate synthetic meshes for insertion via the abdominal route.

Currently, there is no sufficient evidence for other materials.

In assessing the risks associated with mesh insertion, it is important to consider the following aspects:

- Overall surface area of material used (which is greater for POP than for SUI)
- Product design (e.g. physical characteristics of the mesh, size of the pore as a predisposing factor to infection in particular with a pore size less than 75 microns)

  Material (biocompatibility, long-term stability, flexibility, elasticity, aging, etc.). Mesh exposure is only seen with a non-absorbable material such as synthetic mesh.
- The physical properties and durability of the materials, balanced with the unwanted consequences of the material within the tissue on a long-term basis.

Are certain surgery techniques of higher risk? If possible list and describe the risks. (Q2)

All synthetic materials are associated with the risk of mesh exposure. This is clearly demonstrated in animal studies and at 2 years follow-up is evident in 4% of patients.

In general terms, vaginal surgery is associated with a higher risk of mesh related morbidity than abdominal insertion of mesh.

Risk assessment of the use of mesh needs to differentiate between its use for different indications (e.g. SUI, POP).

The SCENIHR acknowledges the efficacy and use of implanted meshes for SUI but recognising the absence of long-term data, it considers that associated risk to be limited. The complications associated with mesh insertion are related to the route of insertion.

The SCENIHR acknowledges that vaginally implanted mesh for POP is associated with increased risks compared to mesh implantation for SUI. Its use should be restricted to patients defined according to established evidence-based clinical guidelines.

Are any combinations of the above (designs / materials and surgical techniques) of a higher risk? (Q3)

Vaginal insertion of non-absorbable synthetic mesh with a large surface area is associated with the highest incidence of complications.

Vaginal insertion of non-absorbable synthetic mesh is associated with a higher complication rate than trans-abdominal insertion.

Are there specific limitations (e.g. clinical, designs / materials, surgical techniques) to the use of meshes in urogynecological surgery? (Q4)

- The evidence available would suggest that the use of xenograft and allograft materials is associated with a high failure rate.
- The risk of use of a synthetic non-absorbable mesh increases with the surface area.

- Material (biocompatibility, - tissue integration, long-term stability and mechanical responses over time (flexibility, elasticity and resistance to deformation).
- Patient characteristics will have an influence on efficacy and potential complications.

What are the risks of surgical interventions using mesh compared to classic surgical interventions? (Q5)

When treating SUI, sling procedures are associated with more storage and voiding symptoms than other repositioning procedures. The use of synthetic non-absorbable mesh is associated with a risk of mesh exposure.

When treating POP by vaginal route, the use of synthetic non-absorbable mesh is associated with a risk of mesh exposure and de novo prolapse of the untreated vaginal compartment as well as the development of de novo stress urinary incontinence. The risk of mesh exposure is reduced when using the transabdominal route considering the different indications for transabdominal or transvaginal POP repair as indicated in the current guidelines.

What factors could affect the outcome of the surgical interventions? (Q6)

The factors influencing the surgical outcomes are:

- Material (biocompatibility, -tissue integration, long-term stability and mechanical responses over time (flexibility, elasticity and resistance to deformation
- Product design (e.g. physical characteristics of the mesh, size of the pore as a predisposing factor to infection in particular with a pore size less than 75 microns)
- Overall mesh size (surface area) of material used (which is greater for POP than for SUI)
- Route of implantation, (e.g., vaginal or trans abdominal)
- Patient characteristics (e.g., obesity, smoking)
- Associated procedures (e.g., hysterectomy)
- Surgeon’s experience

SCENIHR acknowledges the importance of established guidelines, clinical experience and adequate training of the surgeon as well as the need to improve the design of the device to be suitable for use in the pelvic floor which appears to be a more demanding environment than the abdomen (where the same non-degradable meshes have a low complication rate).

5.1.2. Identification of high risk patient groups

Are there patients groups (e.g. in relation to age, weight or other comorbidities) for which the use of meshes would carry a specific risk? (Q7)

The SCENIHR acknowledges the importance of the identification of high-risk patient groups. It is recognised that smoking is statistically associated with increased risk of mesh exposure. However, other factors such as age and obesity may also be important. This should be investigated further.

Taking into account the lack of long-term data on performance and safety of the use of synthetic non-absorbable mesh for POP repair, SCENIHR recommends being more reluctant to use these in younger age groups.

In the light of the above, identify risks associated with use(s) of meshes other than for urogynecological surgery and advise if further assessment in this field(s) is needed. (Q8)

The SCENIHR notes there is limited information in the existing literature on the subject. There is a suggestion that morbidity is associated with colorectal use of meshes. This needs to be quantified by further research before any comment can be made.

5.2. Recommendations

- Ensure the patients are correctly and comprehensively informed relating to the performance and risks associated with synthetic non-absorbable meshes
- Establish European implant registries
- Establish scientific studies to assess the long-term (at least 5 years) safety and performance of the synthetic non-absorbable meshes
- Support further research into novel new materials, in particular absorbable meshes
- Support further research into the application of regenerative medicine technology, such as the cellular seeding of graft materials
- Establish evidence based European Guidelines
- Develop training programs for surgeons in association with European medical associations

6. MINORITY OPINION

None.

7. ABBREVIATIONS AND GLOSSARY OF TERMS

Amid Classification: The classification of materials used for Hernia repair based on their pore size, as reported in: Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia. 1997. 1:15-21

BOO: bladder outlet obstruction

EAU: European association of urology

ICS: international continence society

MUS: mid-urethral slings

OAB: overactive bladder

POP: pelvic organ prolapse

ppd: pads per day

RCT: randomised controlled trial

RP: retropubic

SIMS: single-incision mini-sling

SIS: single-incision sling

SMUS: standard mid-urethral sling

SUI: stress urinary incontinence

TO: transobturator

TOT: transobturator tape

TVT: tension-free vaginal tape

8. APPENDIX

Table 4: Studies on host response to autologous fascia.

Author	Sample	Biomechanical Properties	Host Response
(Fitzgerald *et al.*, 2000)	Autologous rectus fascia implanted in 5 patients suffering from SUI. Samples obtained, respectively, from transvaginal revision after 3, 5, 8 and 17 weeks and from replacement after 4 years.		- Moderate and uniform infiltration of host fibroblasts and neovascularisation after 5 and 8 weeks implantation. - After 4 years implantation, no evidence of inflammatory cell infiltrate or foreign body reaction and collagen remodelling by connective tissue organised longitudinally.
(Jeong *et al.*, 2000)	Autologous lata fascia implanted in 16 rabbits randomised into 4 survival groups and examined after 1, 2, 4 and 8 weeks. Implantation into upper eyelids.		- Low inflammatory cell infiltration. - Fibroblast infiltration and collagen remodelling.
(Choe *et al.*, 2001)	Dermis, rectus fascia and vaginal mucosa harvested from 20 women undergoing vagina prolapse surgery.	Tensiometric analysis of full strips vs. patch suture slings. Displacement and maximum load calculated.	
(Kim *et al.*, 2001)	Autologous rectus fascia implanted in 20 rats randomised into 2 survival groups (2 and 4 months).	No significant decrease of the fracture toughness calculated by the trouser tear test over 4 months.	
(Dora *et al.*, 2004)	Autologous rectus fascia implanted in 15 rabbits randomised into 3 survival groups (2, 6 and 12 weeks). Implantation on the anterior rectus fascia.	No significant decrease of biomechanical properties after 12 weeks implantation.	- 50% decrease in surface area.
(Hilger *et al.*, 2006)	Autologous rectus fascia implanted in 20 rabbits randomised into 2 survival groups (6 and 12 weeks). Half implanted on the rectus fascia and half on the posterior vagina fascia.	No significant decrease of biomechanical properties after 12 weeks implantation.	- Collagen remodeling by moderate collagen infiltration but encapsulation as well. - Minimal inflammatory response. - Minimal neovascularisation.
(Krambeck *et al.*, 2006)	Autologous rectus fascia implanted subcutaneously on the anterior rectus fascia of 10 rabbits randomised into 2 survival groups (6 and 12 weeks).		- Moderate fibrosis. - High degree of scar. - High degree of inflammatory infiltrate.

Author	Sample	Biomechanical Properties	Host Response
(Maia de Almeida *et al.*, 2007)	Adult female rats incontinence model. Marlex, autologous sling, SIS, polypropylene mesh and Sham at 30 and 60 days.		- Reduced inflammatory response and collagen production around autologous grafts, in comparison with synthetic materials and xenografts.
(Woodruff *et al.*, 2008)	Autologous fascia grafts explanted after sling revision from 5 women, due to different complications, between 2-65 months after implantation.		- Moderate and uniform infiltration of host fibroblasts and little neovascularisation. - Collagen remodeling by new collagen fibres organised longitudinally. - No evidence of encapsulation or gross infection.
(Pinna *et al.*, 2011)	Autologous fascia lata implanted in 14 rabbits randomised into 2 survival groups (30 and 60 days). Implantation into the right voice muscle.		- No significant inflammatory reaction. - No significant fibrosis or scarring.

1

2 Table 5: Studies on host response to allografts.

Author	Sample	Biomechanical Properties	Host Response
(Sclafani *et al.*, 2000)	Human cadaveric dermis (AlloDerm®) disk implanted subdermally behind a patient's ear. Micronised human cadaveric dermis (AlloDerm®) injected intradermally and subdermally in 2 different locations behind a patient's ear. Both implants examined 3 and 1 month after implantation, respectively.		- Both materials extensively invaded by host fibroblasts. - Both materials present new collagen in-growth.
(Kim *et al.*, 2001)	Human cadaveric fascia implanted in 20 rats randomised into 2 survival groups (2 and 4 months).	No significant decrease of the fracture toughness calculated by the trouser tear test.	
(Walter *et al.*, 2003)	Freeze-dried and gamma-irradiated human cadaveric lata fascia implanted in 18 rabbits and excised 12 weeks after implantation.	Significant decrease of biomechanical properties after 12 weeks implantation.	
(Spiess *et al.*, 2004)	Human cadaveric fascia lata implanted subcutaneously on the abdominal wall of 20 rats randomised into 2 survival groups (6 and 12 weeks).	No significant decrease of tensile strength with time.	

Author	Sample	Biomechanical Properties	Host Response
(Yildirim *et al.*, 2005)	Human cadaveric lata fascia implanted in 20 rabbits randomised into 4 survival groups (2, 7, 15 and 30 days). Implantation subcutaneously on the abdominal wall.		- Acute inflammation by high cell infiltration predominantly of polymorphous granulocytes. - Integration in host tissue by moderate fibrotic process and muscle infiltration on day 30, with persistent inflammatory response.
(Krambeck *et al.*, 2006)	Cadaveric fascia lata implanted subcutaneously on the anterior rectus fascia of 10 rabbits randomised into 2 survival groups (6 and 12 weeks).		- Moderate to high focal fibrosis. - Minimal to moderate degree of scar. - High degree of inflammatory infiltrate.
(Hilger *et al.*, 2006)	Human cadaveric dermis and lata fascia implanted in 20 rabbits randomised into 2 survival groups (6 and 12 weeks). Half implanted on the rectus fascia and half on the posterior vagina fascia.	Very significant decrease of biomechanical properties after 12 weeks implantation.	- 2 missing or fragmented materials implanted on the vagina after 12 weeks. - Moderate inflammatory response. - Minimal neovascularisation. - Minimal collagen ingrowth without significant cell infiltration.
(Woodruff *et al.*, 2008)	Human cadaveric dermis slings explanted after revision from 2 women, due to different complications, between 2-65 months after implantation.		- Moderate levels of encapsulation. - High levels of degradation. - Peripheries of the grafts invaded by fibroblasts but central portions remained acellular.
(VandeVord *et al.*, 2010)	Human cadaveric dermis and fascia lata implanted in 16 rats, respectively and both randomised into 4 survival groups (2, 4, 8, 12 weeks). Implantation around the bladder neck, anchored to the surrounding tissues.		- Thin fibrous capsule formation. - Moderate cell infiltration and angiogenesis.
(Rice *et al.*, 2010)	Human cadaveric dermis (AlloDerm®) implanted in 18 rats randomised into 2 survival groups (30 and 60 days). Implantation subcutaneously on abdominis rectus muscle defect.	Increase of tensile strength after 30 days and, again, increase of tensile strength after 60 days respectively to 30 days.	- Moderate amounts of collagen deposition well organised. - Abundant revascularisation.
(Kolb *et al.*, 2012)	Human cadaveric dermis (AlloDerm®) implanted subcutaneously in 5 pigs randomised into 4 survival groups (7, 21, 90 and 180 days).		- Robust inflammatory response after 7 days implantation, which achieved maximal level at 21 days, with formation of granulomas and areas of necrosis noted within the graft. - Moderate fibroblast infiltration, collagen in-growth and

Author	Sample	Biomechanical Properties	Host Response
			neovascularisation. - Moderate levels of encapsulation.

1

2 Table 6: Studies on host response to xenografts.

Author	Sample	Biomechanical Properties	Host Response
(Badylak *et al.*, 2001)	Abdominal wall defect repaired with SIS in 40 dogs randomised into 8 survival groups (1, 4, 7 and 10 days; and 1, 3, 6 and 24 months).	Strength was decreased from day 1 to day 10 after implantation, followed by a progressive increased, until double of the original strength 24 months after implantation.	- Rapid degradation with subsequent host remodeling.
(Badylak *et al.*, 2002)	Abdominal wall defect repaired with SIS in 10 dogs and 30 rats, both, randomised into 4 survival groups (1 week, 1 month, 3 months, 6 months and 2 years).		- No shrinkage or expansion of the graft site over the 2-year period of the study. - 1 week after implantation, abundant levels of poly-morphonuclear leukocytes diminished to negligible after 1 month. - Moderate neovascularisation. - By 3 months, graft material was not recognisable and was replaced by moderately well-organized host tissues including collagenous connective tissue, adipose tissue and skeletal muscle.
(Cole *et al.*, 2003)	SIS removed from a 42-years-old female patient 4 months after pubovaginal implantation of the sling due to severe obstruction.		- Completely intact acellular sling. - Well defined fibrous capsule. - Chronic inflammatory response.
(Zhang *et al.*, 2003)	SIS implanted in the abdominal wall of rats for up to 2 months.	SIS together with the abdominal wall have increased strength.	Levels of Interleukin 2 and 6 were high straight after the operation but they become normal after 2 months.
(Wiedemann and Otto, 2004)	Biopsies taken from the implantation site of the SIS band under the vaginal mucosa from 3 patients during re-operation, at a mean of 12.7 months, after pubourethral sling procedures due to recurrent urinary stress incontinence.		- Focal residues of SIS implant. - No evidence of a specific tissue reaction that might point to a foreign body reaction. - No evidence of any significant immunological reaction and in particular no evidence of any chronic inflammatory reaction.
(Konstantinovic *et al.*, 2005)	Abdominal wall defect repaired with SIS in 24 Wistar rats randomised into 4 survival groups (7, 14, 30 and 90 days).	Significant increase of biomechanical properties after 90 days implantation.	- Moderate acute inflammatory response at day 7, decreased to minimal after 90 days. - Moderate neovascularisation.

Author	Sample	Biomechanical Properties	Host Response
			- Abundant collagen deposition well organised after 90 days.
(Macleod *et al.*, 2005)	SIS and cross-linked porcine dermis (Permacol®) implanted subcutaneously on the anterior rectus fascia of 18 rats each randomised into 5 survival groups (1, 2, 4, 10 and 20 weeks).		For both grafts: -No evidence of acute inflammatory response. - From moderate chronic inflammation after 1 week implantation to minimal after 20 weeks. - No evidence of eosinophilic infiltration and stromal fibroblastic reaction over the entire implantation. - Moderate fibrosis and vascularity around the grafts after 1 week implantation to minimal after 20 weeks.
(Poulose *et al.*, 2005)	12 female pigs were implanted with SIS intraperitoneally for up to 6 weeks.		- Cell infiltration - Vascularisation - Collagen deposition and remodelling
(Thiel *et al.*, 2005)	SIS implanted subcutaneously on the abdominal wall of 30 rats randomised into 3 survival groups (7, 30 and 90 days).		- Moderate inflammatory reaction increased to severe after 90 days. - 86% of the graft replaced by new collagen fibres.
(Krambeck *et al.*, 2006)	SIS and porcine dermis implanted subcutaneously on the anterior rectus fascia of 10 rabbits randomised into 2 survival groups (6 and 12 weeks).		- Porcine dermis presented moderate fibrosis which was minimal for SIS. - Minimal degree of scar for both grafts and high degree of inflammatory infiltrate.
(Ko *et al.*, 2006)	Abdominal wall defect repaired with 8-layer SIS in 20 domestic pigs randomised into 2 survival groups (1 and 4 months).	No significant changes of biomechanical properties after 4 months implantation.	- Dense fibrous connective tissue ingrowth. - Minimal to mild mononuclear inflammatory cell infiltrate throughout the connective tissue.
(Hilger *et al.*, 2006)	Porcine dermis implanted in 20 rabbits randomised into 2 survival groups (6 and 12 weeks). Half implanted on the rectus fascia and half on the posterior vagina fascia.	Very significant decrease of biomechanical properties after 12 weeks implantation.	- 2 missing or fragmented materials 12 weeks after being implanted on the vagina. - Moderate to strong inflammatory response. - Minimal collagen ingrowth without significant cell infiltration. - Minimal neovascularisation.
(Kim *et al.*,	SIS implanted in the subcutaneous dorsum of 3		- Prominent infiltration and ingrowth of host cells.

Author	Sample	Biomechanical Properties	Host Response
2007)	rats sacrificed after 2 weeks.		- Few macrophages infiltrated or accumulated around the grafts.
(Rauth *et al.*, 2007)	SIS implanted on the peritoneal surface of the abdominal wall of 6 pigs sacrificed 8 weeks after implantation.		- 80% of contraction from original surface area. - Moderate neovascularisation. - Densely populated by host cells with moderate amounts of new disorganised collagen deposition.
(Woodruff *et al.*, 2008)	Porcine dermis slings explanted after revision from 4 women, due to different complications, between 2-65 months after implantation.		- Severe encapsulation. - No degradation. - No fibroblast infiltration or neovascularisation.
(Sandor *et al.*, 2008)	Abdominal wall defect repaired with SIS and cross-linked porcine dermis (Permacol®) in 33 primates randomised into 3 survival groups (1, 3 and 6 months).		- Considerable contraction after 1 month for both materials, but no significant change over the next 5 months. - Better integration of both materials at late stage by scar formation. - Inflammatory cell infiltration 3 months after implantation for SIS and formation of few blood vessels. - Acellular porcine dermis over the entire course of implantation with substantial inflammation surrounding their perimeter. - Partial resorption for both materials after 6 months.
(Pierce *et al.*, 2009b)	Cross-linked porcine dermis implanted on the abdominal wall and posterior vagina of 18 rabbits sacrificed 9 months after implantation.	11 grafts remained intact without significant changes of biomechanical properties compared to the baseline values. They just were thicker and tolerated less elongation at failure. 7 grafts were partially degraded but thicker again and with significant decrease of all biomechanical properties.	- Host connective tissue incorporation between fibres. - Intense foreign body reaction in degraded grafts which may be expedited in vaginal environment.
(VandeVord *et al.*, 2010)	SIS and porcine dermis implanted in 16 rats, respectively and both randomised into 4 survival groups (2, 4, 8, 12 weeks). Implantation around the bladder neck, anchored to the surrounding tissues.		- Thin fibrous capsule formation. - Moderate cell infiltration and angiogenesis for SIS and minimal for porcine dermis.

Author	Sample	Biomechanical Properties	Host Response
(Rice *et al.*, 2010)	Abdominal wall defect repair with SIS (Surgisis®) in 18 rats randomised into 2 survival groups (30 and 60 days).	Increase of tensile strength after 30 days and, again, increase of tensile strength after 60 days respectively to 30 days.	- Moderate amounts of collagen deposition well organised. - Abundant revascularisation.
(Deprest *et al.*, 2010)	13 patients underwent secondary sacrocolpopexy because of failure or vaginal revision because of a graft related complication after the initial sacrocolpopexy with porcine dermal collagen (Pelvicol®) (9) or SIS (Surgisis®) (4).		- Pelvicol presented high degradation rates associated with no body foreign reaction. - Pelvicol remnants were integrated into collagen rich connective tissue with limited neovascularisation (scar host tissue). - No significant body foreign reaction to Surgisis grafts. - Surgisis no longer recognisable replaced by irregularly organised connective tissue and fat tissue.
(Liu *et al.*, 2011)	Abdominal wall defect repaired with SIS and acellular porcine dermal matrix in 50 Sprague Dawley rats randomised into 5 survival groups (1, 2, 4, 8 and 12 weeks).	After initial decrease of biomechanical properties at week 2, these were increased over the next 10 weeks reaching similar values from week 1.	- Pronounced inflammatory response 1 to 4 weeks after implantation for SIS compared with porcine dermal, but fell to similar negligible values for both after 12 weeks. - Large neovascularisation and collagen deposition, which was higher for SIS group. - SIS implants degraded more quickly and were almost totally replaced by organised collagenous tissues. - Contraction at first weeks leading to significant lower surface area in both materials.
(Jenkins *et al.*, 2011)	Abdominal wall defect repaired with porcine dermal matrix in 24 Yucatan mini pigs randomised into 2 survival groups (1 and 6 months).	Significantly greater incorporation strengths after 6 months compared with 1 month.	- Moderate cell infiltration. - Moderate extracellular matrix deposition. - Moderate neovascularisation. - Partial degradation and from widely to mild fibrous encapsulation.
(Kolb *et al.*, 2012)	Cross-linked porcine dermis (Permacol®) implanted subcutaneously in 5 pigs randomised into 4 survival groups (7, 21, 90 and 180 days).		- Mild inflammatory response decreased to minimal from day 7 to day 180 after implantation. - None to minimal neovascularisation after 180 days. - Small amount of residual SIS remained were surrounded by mild to moderate chronic inflammation.

Author	Sample	Biomechanical Properties	Host Response
			- Moderate levels of encapsulation.
(Daly *et al.*, 2012)	Abdominal wall defect repaired with porcine dermis in rats randomised into 3 survival groups (1, 3 and 35 days).		- Cell infiltrate into entire grafts by day 35. - Degradation of the scaffold most pronounced at the periphery with fibrous tissue, angiogenesis and foreign body giant cells noted. - Grafts surrounded by a dense and circumferentially organised connective tissue. - Mononuclear cells decreased in number compared with earlier time points.

1

2 Table 7: Studies on host response to polypropylene meshes.

Author	Sample	Biomechanical Properties	Host Response
(Falconer *et al.*, 2001)	16 women were implanted with TVT for up to 2 years: 6 with Mersilene and 10 with Prolene.		Mersilene induces higher inflammatory response than Prolene. Mersilene is easier to extract than Prolene.
(Klinge *et al.*, 2002)	heavy weight monofilament with small pore size (HWM) and low weight with large pore size multifilament (LWM) on the posterior abdominal wall of rats for 7, 14, 21 and 90 days.		HWM: intense inflammation, embedded in connective tissue. LWM: less pronounced inflammatory response and fibrotic capsule, collagen distributed within the mesh
(Wang *et al.*, 2004)	17 women with sling erosion and 7 women with voiding difficulties implanted with TVT and SPARC.		Pronounced fibrosis around the fibres – erosion and voiding difficulty as a result
(Rabah *et al.*, 2004)	Implantation of Surgipro and Cadaveric fascia lata in rabbit's bladder neck for 6 and 12 weeks.		Cadaveric fascia lata group: the implant was incorporated in a plate of fibrous tissue. Polypropylene mesh: inflammation localised on the graft.
(Spiess *et al.*, 2004)	TVT and Cadaveric fascia lata implanted in rats abdominal wall for 6 and 12 weeks.	TVT has the greater break load and the maximum average load compared to Cadaveric Fascia Lata.	
(Zheng *et al.*, 2004)	Prolene and Pelvicol implanted in full thikness abdominal wall defects in rats for 7, 14, 30 and 90 days.		Prolene prosthesis show the presence of leukocytes in the activated state.

Author	Sample	Biomechanical Properties	Host Response
(Konstantinovic *et al.*, 2005)	Marlex and non-cross-linked Surgisis implanted on the anterior abdominal wall of rats for 7, 14, 30 and 90 days.		Marlex: more pronounced inflammatory reaction and vascularisation throughout the graft that Surgisis Surgisis: milder inflammatory reaction.
(Yildirim *et al.*, 2005)	Gynecare TVT, SPARC™, polypropylene mesh and IVS implanted in contact with the rats rectus muscle for up to 30 days.		Inflammation and fibrosis are decreased in large pore meshes.
(Thiel *et al.*, 2005)	Monofilament Polypropylene mesh, silicone mesh, SIS and PLA were implanted subcutaneously on the abdomen of rats for 7, 30 and 90 days.		Polypropylene induces the mildest inflammatory response among the samples.
(Bogusiewicz et al., 2006)	Monofilament TVT and multifilament IVS were implanted in rats rectus fascia for 42 days.		They induce production of similar amount of collagen Differences in the arrangement of collagen and inflammation intensity
(Boulanger et al., 2006)	Vicryl, Vypro, Prolene, Prolene Soft and Mersuture were implanted in pgs peritoneum for 10 weeks.		Vicryl: low level of inflammation and completely absorbed. Vypro: intense inflammation and strong fibrotic response. Prolene and Prolene Soft: well integrated, weak inflammatory response. Mersuture: no good integration.
(Krambeck *et al.*, 2006)	SPARC mesh,human cadaveric fascia, porcine dermis, SIS and autologous fascia were implanted in rabbits rectus fascia for 12 weeks.		Polypropylene mesh has the greatest scar formation. Polypropylene has the mildest inflammatory response.
(Boukerrou *et al.*, 2007)	Pre-peritoneal implantation of Vicryl, Vypro, Prolene, Prolene Soft and Mersuture mesh for 2 months in pigs.	Non-absorbable, monofilamentous, macroporous materials (type I) seem more resistant, retract less and has the best tolerance.	
(Spelzini *et al.*, 2007)	Polypropylene type I mesh and Macroporous silk construct were implanted in rat fascial defects for 7, 14, 30 and 90 days.		Polypropylene meshes induce a moderate inflammatory response and not architectural degradation.
(Zorn *et al.*, 2007)	Rat abdominal wall was implanted with SPARC™, TVT and SIS for 6 weeks, 9,	TVT has tensile properties similar to SPARC and They are superior to	

Author	Sample	Biomechanical Properties	Host Response
	6, 9 and 12 months.	Stratasis.	
(Bazi *et al.*, 2007)	Rats rectus fascia was implanted with Advantage, IVS, SPARC and TVT for up to 24 weeks.	They all show similar mechanical properties after removal.	They induce different host responses due to different porosity.
(de Tayrac *et al.*, 2007)	Ewes vaginas were implanted with a non-coated LW polypropylene mesh (Soft Prolene) and a coated one (Ugytex) from 1 to 12 weeks.		Similar inflammatory response between the two materials.
(Huffaker *et al.*, 2008)	Rabbits vaginas were implanted with Pelvitex (Collagen-coated) and Gynemesh (uncoated Polypropylene meshes) for up to 12 weeks.		Both materials induce a mild foreign body reaction with minimal fibrosis.
(Woodruff *et al.*, 2008)	24 grafts were explanted in women undergoing sling revision after 2-34 months. Grafts were Polypropylene meshes, autologous fascia, porcine dermis and cadaveric dermis.		No evidences of degradation or encapsulation, abundant host infiltration. Neovascularisation was visible.
(Elmer *et al.*, 2009)	PROLIFT® was implanted in humans for 1 year.		Increase in macrophages and mast cells count. Mild but persistent foreign body response.
(Pierce *et al.*, 2009b)	Polypropylene mesh vs. Cross-linked porcine dermis implanted in rabbits vagina and abdomen for 9 months.		Polypropylene caused milder inflammatory reaction, more long-term, good host tissue incorporation.
(Melman *et al.*, 2011)	Bard® mesh (HWPP), Ultrapro® (LWPP), GORE® Infinit mesh (ePTFE) in an mini-pigs hernia repair for 1, 3 and 5 months.	Their maximum tensile strength decreases for all of them.	Inflammation decreases with time. Cell infiltration increases with time.
(Pascual *et al.*, 2012)	Surgipro, Optilene, GORE® Infinit mesh (ePTFE) were implanted in rabbits abdominal wall defect for 14 days.	LWPP implants might be improved by the newly formed tissue around it.	PTFE induces an increased macrophage response when compared to polypropylene. Increase collagen deposition in high porosity meshes.
(Manodoro *et al.*, 2013)	Gynemesh in two sizes (50x50 mm and 35x35 mm) implanted in 20 adult ewes for 60 and 90 days, both on the abdominal and vaginal walls.	Implants were contracting more when implanted on the vaginal wall, compared to abdominal wall. Grafts implanted on the vaginal wall are stiffer than the ones implanted	30% of the 50x50 meshes caused vaginal erosion and exposure. 60% of the 35x35 meshes had reduced surface (i.e. contracting after 90 days.

Author	Sample	Biomechanical Properties	Host Response
		on the abdominal wall, after retrieval.	

HWPP – heavy weight polypropylene

LWPP – lightweight polypropylene (also called soft) / ePTFE – expanded polytetrafluoroethylene /

PLGA – poly lactide-co-glycolide acid / PLA – poly lactide acid / PGA – poly glycolide acid

Table 8: Classification of synthetic materials used in pelvic floor reconstruction.

Type	Mesh Pore size	Structure	Polymer	Trade name	Company
I	Macroporous > 75 µm	Monofilament	Polypropylene	Uretex®	CR Bard
				Gynecare TVT	Ethicon, Johnson&Johnson
				Bard® Mesh	Bard/Davol
				SPARC™	American Medical Systems
				In-Fast™	American Medical Systems
				Monarc™	American Medical Systems
				Lynx®	Boston Scientific
				Advantage®	Boston Scientific
				obtryx®	Boston Scientific
				Optilene®	B. Braun
				Aris™	Mentor Corp
				Perigee™	American Medical Systems
				Parietene	Covidien
				Intepro®	American Medical Systems
				Gynecare Prolift®	Ethicon, Johnson&Johnson
				Surgipro™	Covidien
				Prolene®	Ethicon,

Type	Mesh Pore size	Structure	Polymer	Trade name	Company
					Johnson&Johnson
				Prolene® Soft	Ethicon, Johnson&Johnson
				Gynemesh PS	Ethicon, Johnson&Johnson
				Atrium	Atrium Medical
				Marlex®	CR Bard
		Multifilament	Copolymer of glycolide (90%) and lactide (10%)	Vicryl®	Ethicon, Johnson&Johnson
				Vypro®	Ethicon, Johnson&Johnson
			Polypropylene and Polyglecaprone	UltraPro®	Ethicon, Johnson&Johnson
			Poly Glycolic Acid	Dexon®	Davis and Geck
II	Macroporous < 10 μm	Multifilament	Expanded PTFF	GoreTex®	W.L Gore
			Poly Ethylene Terephtalate	Mersuture	Ethicon, Johnson&Johnson
III	Macroporous with microporous components < 10 μm	Multifilament	PTFE	Teflon®	C.R. Bard
			Poly Ethylene Terephtalate	Mersilene®	Ethicon, Johnson&Johnson
			Polypropylene	IVS Tunneller™	Tyco Healthcare
			Woven polyester	Protegen	Boston Scientific
IV	Nanoporous < 1 μm	Multifilament	Silicon-Coated Polyester	Intemesh®	American Medical Systems
			Dura Mater substitute	PRECLUDE® MVP® Dura substitute	W.L. Gore
			Expanded PTFE, pericardial membrane substitute	PRECLUDE® Pericardial Membrane	W.L. Gore

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