

## **AUGS Testimony for FDA Panel on Trans-vaginal Mesh for the Anterior Wall**

At the American Urogynecologic Society (AUGS), we respect the vital role of the FDA in ensuring that our patients have access to medical devices that are efficacious, safe and meet their health care needs. We also respect the FDA's leadership over the past decade in pursuing this mandate within Urogynecology. The FDA's early recognition of risks associated with trans-vaginal mesh, first identified in 2008, and then expanded in the 2011 **FDA Safety Communication**, were important counters to inadequacies in the scientific development and early regulation of these devices.[1] Moreover, the decision in January of 2016 to reclassify surgical mesh for trans-vaginal repair of pelvic organ prolapse as Class III, paved the way for the necessary premarket assessment of these devices. We are honored to attend the **Advisory Committee Meeting** scheduled for February 12, 2019 to contribute to the evaluation of the benefits and risks associated with mesh medical products for treatment of anterior wall pelvic organ prolapse (POP), towards defining the appropriate population of women for whom this is a reasonable option.

### Executive Summary

At AUGS, we look forward to learning the results of the 522 studies, and in this testimony will offer some specific suggestions about interpretation of results. Even at their best, though, studies such as the 522 studies are not able to address several important areas:

- Patient characteristics, including recurrent prolapse
- Outcomes reported directly by the patient
- Longitudinal follow-up, again directly from the patient
- Surgeon characteristics, including training, experience and volume

All of these, and other considerations, will continue to inform the use of trans-vaginal mesh for POP, and to provide better surveillance and assessments of their use in specific circumstances

### Introduction

AUGS supports the continued development and availability of trans-vaginal mesh devices for the treatment of POP. We acknowledge the safety concerns around these devices, although would like to take the opportunity to clarify that these relate to local anatomic issues regarding tissue incorporation, scar formation, and mesh exposure/erosion. Claims of *systemic* complications have *not* been supported scientifically. Mesh does *not* cause cancer. A Swedish health care registry examined over 5 million women over the age of 18 years, including 20,905 women who had a mid-urethral sling, and 238,476 women that had cancer (from 24 different organ systems), and there was no associations between mesh use and cancer.[2] Similarly, mesh does

*not* cause auto-immune disease, as demonstrated by a study that showed no link between mesh use and auto-immune disease.[3]

This document will offer considerations of how to evaluate trans-vaginal mesh procedures for POP for safety and efficacy. It will also lay out some of the programs and policies that we propose to maximize the safety for their use, improve the availability of well-trained providers who can help them decide if or when to use them, and to more skilfully address the unintended outcomes associated with their use. AUGS feels that women are better served when there are more treatment options, and trans-vaginal mesh for prolapse is a very reasonable and possibly advantageous option for women to consider under certain conditions

### Indications for Trans-vaginal Mesh in POP Repairs

All surgical interventions offer benefit to the patient that must be balanced by the potential risk inherent to the intervention. The probability of benefit varies by procedure, patient, and surgeon, as does the type of complication and probability of a complication. In considering a potential treatment, patients should personally balance the probability of benefit with the potential risk of complications. Moreover, the evaluation of potential complications should not only consider the frequency of occurrence, but also the degree of associated morbidity, and the degree of difficulty of treating them. Providing adequate information to patients to prepare them for these decisions is a responsibility of the physician proposing treatment. Physicians can help to frame the benefits and risks through shared decision-making, but ultimately it is the patient that must make this decision.

Because the balance of benefit and risk is a personal decision, women benefit from having a range of treatment options. This is especially true for the treatment of pelvic floor disorders, where the goal of intervention is to improve the quality of life of the patient. Each individual experiences pelvic floor disorders differently, underlining the need for a spectrum of treatment options, including non-surgical options, which may have decreased efficacy, but balanced against a lower risk of complication. The need for alternative treatments also applies to surgical interventions. Within the epidemiologic literature, the reported rate of reoperation for pelvic organ prolapse is 13% at five years, rising to 17% at ten years. [4,5] Not all patients with recurrence seek additional surgery, so the actual recurrence rate is probably higher. Importantly, the reoperation rate is higher for women who have previously failed a surgery for pelvic organ prolapse (17%) compared to those having their first surgery for POP(12%). [4] This population of women who have already failed a surgery for POP, especially if they are very symptomatic, are examples of patients who may reasonably be willing to assume higher risk of complication for a more durable surgical repair.

AUGS would also like to focus this testimony specifically on the use of trans-vaginal mesh for prolapse. There are three main types of surgical procedures performed with surgical mesh to treat pelvic floor disorders:

- Trans-vaginal mesh to treat POP
- Trans-abdominal mesh to treat POP
- Mid-urethral mesh sling to treat SUI

Each of these procedures has unique profiles of benefit and risk, and it is important not to confuse the procedures and the unique benefits and risks. AUGS agrees with the FDA in the stated aim of this panel to consider the use of trans-vaginal mesh for the treatment of POP only, as the risks and benefits of mesh use in these three categories are substantially different. At the same time, most of the trans-vaginal mesh products presently on the market are used for apical as well anterior POP.

The promise of the trans-vaginal mesh procedure, introduced in the early 2000s for POP, was to achieve the durability of an abdominal mesh procedure, with a less invasive surgical approach, and decrease in complications of the sacral colpopexy related to the abdominal approach. The FDA Safety Announcements in 2008 and 2011 demonstrated that the actual results of the trans-vaginal approach included higher complications than the native tissue repairs and the abdominal mesh repairs, with uncertain improvement in durability.[1] However, the outcomes were different depending on the vaginal compartment where the mesh was used. For example, adding mesh to primary repairs of the posterior vaginal wall increased complications with no improvement in anatomical results or relief of symptoms.[6] Based on this evidence, all of the manufactures ceased marketing trans-vaginal mesh kits for posterior vaginal wall prolapse.

The anterior vaginal wall is the area of greatest vulnerability for native tissue POP repairs. Multiple Randomized Clinical Trials assessing POP procedures using trans-vaginal mesh in the anterior vaginal wall show anatomic benefit, with less evidence of subjective benefit. [6,7] Nevertheless, some patients may decide that the mesh-based complications associated with these procedures are outweighed by the added durability provided by the trans-vaginal mesh. While AUGS does not feel that there is evidence to support the routine use of trans-vaginal mesh for POP, there are certain patient characteristics that increase the potential benefit of the trans-vaginal mesh approach, creating a favourable balance with the increased rate of surgical complications. Specific characteristics include:

- Failed previous native tissue repairs
- Injury to the pelvic floor musculature
- Connective tissue or neurologic disorders, or other medical conditions that may increase the predicated rate of failure
- Medical or surgical issues compromising abdominal access
- Medical advantage for regional anaesthesia

## Optimizing Evidence on the Use of Trans-vaginal Mesh in POP Repairs

While there is adequate data to determine that adding trans-vaginal mesh to a posterior vaginal wall repair for primary prolapse does not improve outcomes and increases complications [6], the evidence for procedures using trans-vaginal mesh to repair the anterior wall and apex are less clear. There are several glaring gaps in the evidence. Firstly, many of the RCTs investigating mesh in the anterior compartment used devices or mesh materials that are no longer available; as material improvements (such as lighter weight, open pore architecture) have taken place, mesh performance has improved, so older data should be applied to newer materials with caution. Each device should be evaluated on its own merit. Moreover, there is a paucity of studies to compare the efficacy and safety in different populations of women, including the risk factors outlined in the previous paragraph. This compromises the ability to compare potential benefits to risks in any given patient. Additionally, best practices and algorithms for categorizing and treating mesh complications have not been well developed, and are often the expert opinion of individual surgeons with variable amounts of experience. Lastly, much of the available data comes from academic centers that may not reflect the real world performance of these products.

## Methodological Considerations for Evaluating Trans-vaginal Mesh in POP Repairs

AUGS supports the use of the FDA benefit-risk framework, that includes 5 key decision factors: Analysis of the Condition, Current Treatment Options, Benefit, Risk, and Risk Management.[8](Table 1) The analysis of the condition and current treatment options provides essential context to weighing the benefits and risks of the treatment under review. Because POP procedures that use mesh offer better durability offset by potentially higher risk of complications, any comparison to traditional native tissue repairs must include assessment of both durability and safety.

**Table 1.** FDA Benefit Risk Assessment Framework

Decision Factor	Evidence	Uncertainties	Conclusions
Analysis of Condition			
Current treatment options			
Benefit			
Risk			
Risk Management			
Benefit-risk Summary Assessment			

Benefit and risk can be summarized from 522 studies, although other considerations, including surgeon characteristics (training, experience and volume) are also necessary. The key considerations of benefit include the analyses of appropriate subpopulations. Key considerations of risk include the severity and reversibility of adverse events. Risk Management assesses the practicality of insuring that the treatment is directed to those patients for whom the risk is considered acceptable. Finally, the model provides a method to draw conclusions based on a standardized subjective assessment of the evidence and uncertainties in each category. Adopting such a benefit risk approach to assessing the trans-vaginal mesh procedures for anterior POP and their success in specific subpopulations is necessary in comparing trans-vaginal mesh procedures to native tissue repairs.

In developing the POP Module of the AQUIRE Registry, AUGS used the Delphi process to identify the most important parameters for assessing treatments of POP, although outcomes for POP surgery are well established by the Pelvic Floor Disorders Network as well. Patients seek treatment for their POP to alleviate symptoms, and this fact underlines the primacy of patient centered outcomes, and ideally, patient-reported outcomes, as the primary outcome measure. Because surgery for POP seeks to impact symptoms by fixing anatomy, anatomical outcomes are frequently used as a proxy outcome. Anatomical outcomes are also favoured as an objective assessment that is valuable for longitudinal analysis; nevertheless, anatomical outcomes should not be used in place of patient centered outcomes.

In seeking patient centered outcomes, there are well-established and validated objective condition specific quality of life measures for POP that should be used to collect this data. These validated quality of life metrics, such as the Pelvic Floor Distress Inventory, and the Pelvic Floor Impact Questionnaire, evaluate prolapse symptoms, as well as urinary and bowel function.[9] Sexual function is also an important aspect of vaginal function that cannot be neglected. There are other parameters aside from POP that influence sexual function, and some patients with POP will not be sexually active due to other reasons. Consequently, while not all subjects need to be sexually active, there must be sufficient numbers to assess sexual function before and after the procedures, and this assessment should use validated clinimetric tools that include desire, arousal, orgasm, and satisfaction, in addition to activity and dyspareunia. [10,11]

In addition to patient centered outcomes and anatomical outcomes, reoperation or retreatment of POP is also a necessary outcome measure. Reoperation is a significant complication given the addition of a new set of perioperative and long-term surgical risks. This applies to reoperation for complications and recurrent POP, although ultimately these may differ in terms of the potential for success of reoperation and the morbidity of the procedure. Assessment of other surgical complications could use the Clavien-Dindo Complication Scale, a general complication scale, or the new condition specific complication scale, the Pelvic Floor Complications Score. [12,13]

Blinded studies minimize the opportunity for bias to confound results but also compromise the external validity of the study. Given the importance of evaluation of procedures in a broad range of surgeons and the feasibility constraints of long-term blinded studies, this may not be an optimal methodology, and highlights the need for a variety of study designs for adequate comparison of mesh based POP procedures to native tissue repairs.[14] Surgical registries offer a real world assessment that compliments randomized trials.

There is ample evidence that mesh exposures are not time limited, but have a cumulative risk.[15] This means that the added durability must continuously be balanced against the cumulative risk of mesh exposure. This fact underlines the importance of long-term studies of 5 to 10 years that assess both efficacy (durability) and safety. Again, the value of a registry for the long-term analysis is clear.

As previously noted, different patients will have different benefit and risk equations, and defining patient subgroups is essential to personalizing the treatment to the patient's wishes. The most important patient characteristics to consider are those parameters that have been shown to increase the risk of recurrent POP or mesh complications. Parameters for recurrent POP include prior failed POP procedure, stage of POP, pelvic floor muscle injury, including avulsion and weakness, and obesity. [16] For mesh exposure, smoking and vaginal atrophy and concurrent hysterectomy need consideration. [17]

Because the current literature does not meet the needs of patients, AUGS promotes the use of a registry for Quality Improvement that will provide valuable information in a real-world, real-time, longitudinal, and patient-based fashion. The AUGS Quality Improvement Registry (AQUIRE) was developed as a quality improvement registry that allows physicians to participate in the Merit-Based Incentive Payment System arm of the Quality Payment Program. As AQUIRE has evolved, its focus and goals have expanded. AQUIRE now aims to collect real-world evidence to drive quality improvement by bringing together urogynecologists, gynecologists, urologists, industry and government agencies, to answer important questions best addressed through broad registry participation and evidence-based medicine. Data collected in AQUIRE will include direct patient-reported outcomes, and will be available to multiple stakeholders, including the FDA and device manufacturers, to meet regulatory and device surveillance requirements, and aid in the improvement of pelvic floor devices. Recognizing that all surgical interventions have complications, AUGS is expanding the registry to include a module dedicated to the management of surgical complications, including mesh complications. This will provide important information to build clinical algorithms to inform physicians on how best to manage these complications with consistency and the best data available. Ultimately, the AQUIRE registry will provide the data to expand physicians' understanding of benefits and risks of specific treatments, including mesh-based treatments, within specific populations. This will allow AUGS to leverage physician education to

enhance patient education and realize personalized management of pelvic floor disorders.

### Education Needs Related to Trans-vaginal Mesh in POP Repairs

AUGS sees a number of specific educational needs, both for patients and their providers, related to trans-vaginal mesh repair for prolapse, and related pelvic floor issues. With respect to patients, they are served by having information about pelvic floor conditions, and treatment considerations that are as individualized as possible. We are actively engaged in the development and use of a shared-decision model that allows patients to choose treatment options aligned with their own values and preferences, guided by the best available data. AUGS has shared-decision grids under development for pelvic floor disorders and they will be valuable in helping patients and their physicians make informed evidence-based decisions.

The primary role of AUGS as a purveyor of surgical education for health care providers is the development and maintenance of competencies in diagnosis and management of pelvic floor disorders. This includes non-surgical and surgical treatments, including those that use mesh and alternative procedures to support patient choice; AUGS believes that these options should be available for all patients, for any pelvic floor condition. It also extends to developing and promoting competencies in managing surgical complications, including those related to mesh.

The noted variation in complications associated with trans-vaginal mesh in POP repairs suggests that there is a spectrum of competency with these procedures. This highlights the importance of improving education and defining credentialing criteria for surgeons learning these techniques. AUGS supports the role of professional organizations in developing and supporting surgical education for both learners and practicing physicians related to trans-vaginal mesh in POP repairs. Our educational mission supports lifetime learning by defining the curriculum for learners and ensuring quality continuing education to support practicing physicians. We believe that surgeons offering trans-vaginal mesh repairs should provide appropriate informed consent that includes discussion of alternative treatments and potential complications, and should monitor their quality through a surgical registry. [18]

There is ample evidence of a direct relationship between surgical volume and surgical quality outcomes. A recent systematic review that incorporated findings from 32 reviews across surgical disciplines of 15 surgical procedures, demonstrated that higher surgical volume was associated with lower surgical complications, blood loss, length of surgical time, length of stay, and cost of surgery.[19] This relationship between volume and quality holds for gynaecology as well. This relationship of surgical volume to quality has been demonstrated in gynecologic laparoscopy and hysterectomy.[19,20] The AUGS Quality Network is presently pursuing such data for urogynecologic surgery, where we assume the relationship also applies. This highlights a shortcoming of the data available from 522 studies that are only drawn from the practices of very

experienced high volume surgeons. True surgical registries, like AQUIRE, offer a broader spectrum of surgeon experience that allows the consideration of surgeon volume as an influence on procedure outcome.

AUGS supports the FDA framework for assessing the benefits and risks of the trans-vaginal mesh procedures for anterior vaginal wall POP within different populations of women suffering from anterior vaginal POP. [8] AUGS believes that women are best served when they have options from which to choose, and well-educated and experienced providers. The approach outlined above will better allow women to make personalized treatment decisions based on evidence. However, it is essential to define medical device safety and appropriate regulation of devices to ensure patient safety. We believe that registries, like AQUIRE, are the most appropriate means to his end. Expanding the AQUIRE registry and using it to enhance patient and physician education are priorities for AUGS.

Finally, AUGS would like to reflect on the recent history, before marketed devices specifically for the placement of trans-vaginal mesh for prolapse were introduced to the FDA. A wide variety of surgeons, seeking to improve on the sometimes frustrating failure rate of native-tissue repairs, were fashioning their own mesh or graft implants in a wide variety of techniques. The variation in approaches compromised efforts to compare techniques, and track outcomes in any meaningful way. The use of registries, such as AUGS' AQUIRE registry, allows for surgeon data, patient information, Unique Device Identifiers (UDIs) and patient reported outcomes to provide robust and meaningful real-world and real-time information. If mesh devices marketed for prolapse were to be removed, we would lose the ability to use Unique Device Identifiers; it is likely that some surgeons would, in their advocacy for their patients, feel the need to return to practice of devising their own techniques, which would curtail our ability to perform device surveillance and benchmarking analyses. AUGS believes this would actually be a disservice to women with pelvic floor disorders, especially for those with native-tissue failures.

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