Surgical Mesh for Transvaginal Repair of Pelvic Organ Prolapse in the Anterior Vaginal Compartment

FDA Executive Summary

Obstetrics and Gynecology Devices Panel
February 12, 2019

Table of Contents

I. Introduction

On February 12, 2019, the Food and Drug Administration (FDA) will convene the Obstetrics and Gynecology Panel (the Panel) of the Medical Devices Advisory Committee to discuss surgical mesh placed transvaginally in the anterior vaginal compartment to treat pelvic organ prolapse.

In September 2011, the FDA convened the Panel to obtain recommendations on the safety and effectiveness of surgical mesh placed transvaginally to treat pelvic organ prolapse, including the need for additional regulatory action. Based on the evidence available at the time, the Panel's consensus was that mesh placed transvaginally to treat pelvic organ prolapse did not have a well-established benefit/risk profile. Based on the Panel's recommendations, the FDA reclassified surgical mesh placed transvaginally to treat pelvic organ prolapse to a higher risk category (class II to class III) and issued postmarket surveillance study orders.

Four postmarket surveillance studies for five surgical mesh devices indicated for transvaginal repair of pelvic organ prolapse are currently ongoing, and there are three currently marketed surgical mesh devices indicated for anterior repair of pelvic organ prolapse transvaginally – Boston Scientific Uphold LITE, Boston Scientific Xenform, and Coloplast Restorelle DirectFix Anterior. The FDA will use the results of the postmarket surveillance studies to evaluate the safety and effectiveness of individual surgical mesh devices placed in the anterior vaginal compartment to treat pelvic organ prolapse and determine if the benefit/risk profile of each device supports continued marketing.

This executive summary provides an overview of the relevant clinical, device, and regulatory background for surgical mesh placed transvaginally in the anterior vaginal compartment. This document also provides an overview of the published literature for these devices. The FDA's review of the published literature focuses on key safety and effectiveness outcomes for surgical mesh placed transvaginally in the anterior vaginal compartment, as well as important patient and surgeon factors. This document also includes an analysis of the adverse event reports received by the FDA through the Manufacturer and User Device Experience (MAUDE) database.

Based on this information, the FDA is seeking Panel input on how to assess the effectiveness, safety, and benefit/risk of mesh placed transvaginally in the anterior vaginal compartment, as well as how to identify the appropriate patient population and physician training needed for these devices. Specifically, the FDA requests Panel input on (1) whether mesh should be more effective than native tissue repair and at what timepoint, (2) if both anatomic and subjective outcomes should be used to assess effectiveness, (3) the types of adverse events that should be used to evaluate safety and how those adverse events should be assessed, (4) whether the adverse event profile of mesh should be similar to native tissue repair and at what timepoint, (5) any special considerations related to the mesh material, (6) effect of patient factors and surgeon training on safety and effectiveness outcomes, and (7) the overall benefit/risk of surgical mesh placed transvaginally in the anterior vaginal compartment to treat pelvic organ prolapse.

The FDA is not asking the Panel to determine the safety and effectiveness of specific devices or surgical mesh placed in the anterior vaginal compartment. Rather, the information from the literature review and MAUDE database are being provided to give context around how the safety and effectiveness of surgical mesh placed transvaginally in the anterior vaginal compartment are typically assessed and the key considerations that affect these outcomes. The FDA intends to use the recommendations from the

Panel to complete its review of the postmarket surveillance study results for the Boston Scientific Uphold LITE, Boston Scientific Xenform, and Coloplast Restorelle DirectFix Anterior.

In the published literature and clinical practice, the term "surgical mesh" may refer to devices made of synthetic materials, and the term "graft" may be used to refer to devices made of biologic material. In this executive summary, the FDA uses the term "surgical mesh" to refer to devices made of synthetic materials or biologic material and specifies where information applies to devices made of one material.

In addition, while the scope of this executive summary is limited to surgical mesh placed in the anterior vaginal compartment, the FDA acknowledges that anterior compartment prolapse often includes an apical component. Therefore, the information described in this executive summary includes anterior/apical compartment repair. The FDA also notes that the three currently marketed surgical mesh devices indicated for anterior repair of pelvic organ prolapse transvaginally are designed to repair both the anterior and apical compartments.

II. Clinical Background on Pelvic Organ Prolapse

A. Overview of Condition

Pelvic organ prolapse (POP) occurs when the tissue and muscles of the pelvic floor no longer support the pelvic organs, resulting in the prolapse (drop) of pelvic organs from their normal position. Organs involved may include the vagina, cervix, uterus, bladder, urethra and/or rectum.

Figure 1 depicts normal pelvic anatomy. Depending on where weakness occurs, POP can occur in one or more compartments of the vagina, including the bladder (cystocele) (**Figure 2**), the uterus (**Figure 3**), the rectum (rectocele) (**Figure 4**), the top of the vagina (apical prolapse) or the bowel (enterocele). The most common condition in cases of POP is cystocele (anterior wall prolapse), but multiple compartments may be involved [1].

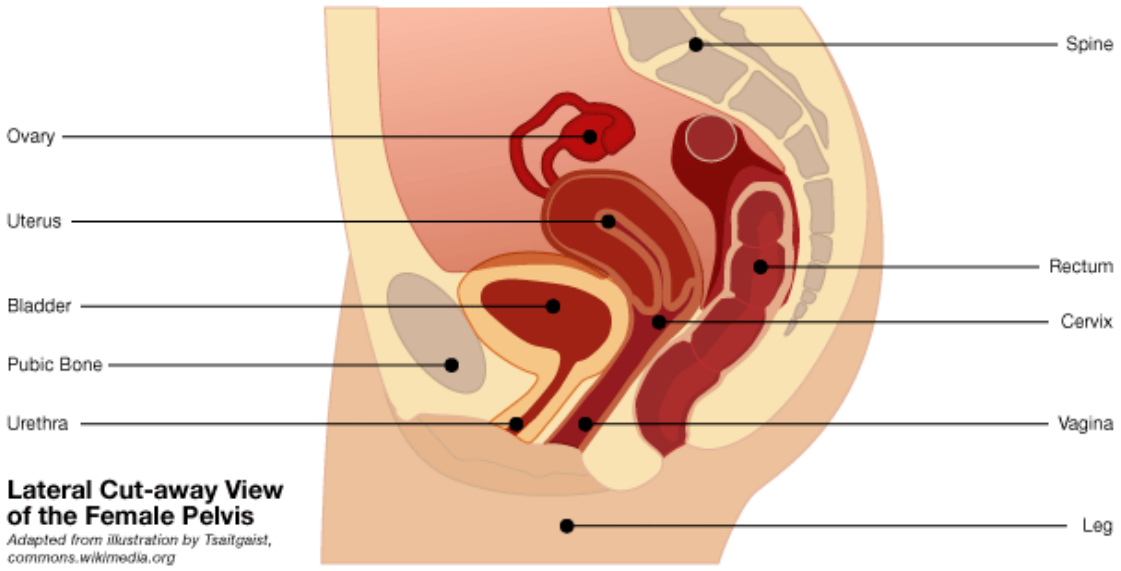


Figure 1 – *Normal Pelvic Anatomy.* *This image is a lateral cut-away view of the female pelvis depicting normal anatomy. The vagina, cervix, uterus, ovary, urethra, bladder, rectum, pubic bone, spine, and leg are labelled.*

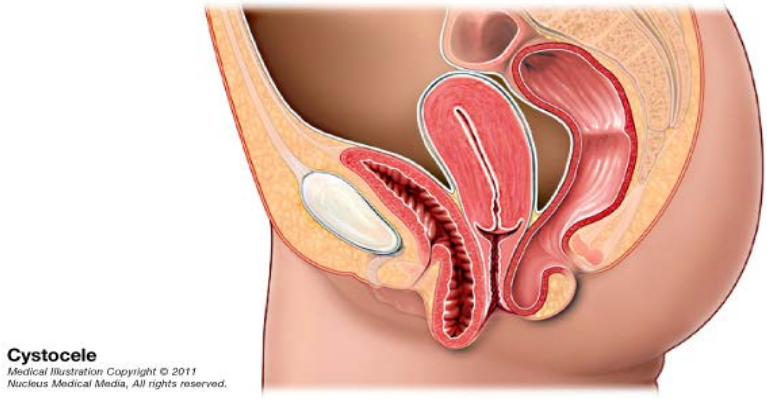


Figure 2 – *Cystocele.* *This image is a lateral cut-away view of the female pelvis depicting cystocele. In this image, the bladder has prolapsed past the vaginal introitus. The uterus and rectum have also prolapsed from their normal positions.*

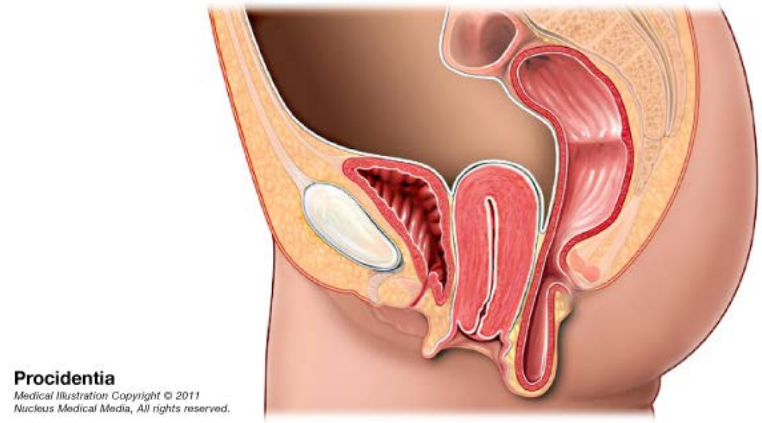


Figure 3 – *Uterine Prolapse.* *This image is a lateral cut-away view of the female pelvis depicting uterine prolapse. In this image, the uterus has prolapsed into the vaginal introitus. The bladder and rectum have also prolapsed from their normal positions.*

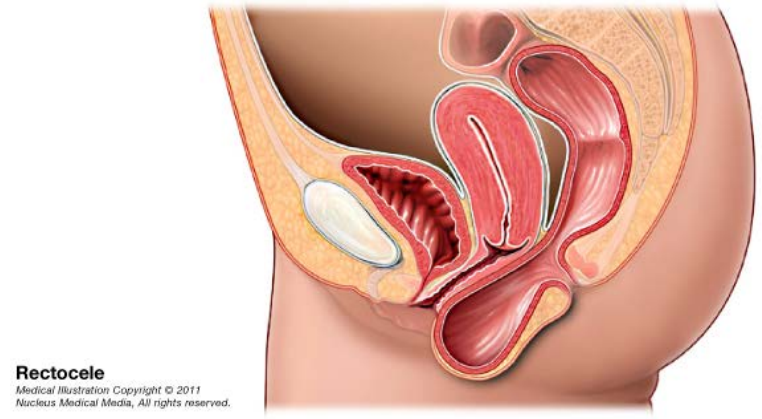
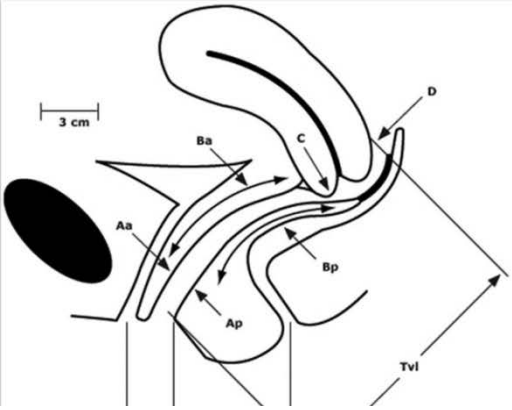


Figure 4 – *Rectocele.* *This image is a lateral cut-away view of the female pelvis depicting rectocele. In this image, the rectum has prolapsed past the vaginal introitus. The bladder and uterus have also prolapsed from their normal positions.*

The Pelvic Organ Prolapse Quantification (POP-Q) system is commonly used to describe the degree of prolapse. The degree of prolapse is described in stages from 0 to 4, with higher numbers indicating more severe prolapse. Higher stages are more likely to be symptomatic [2]. POP-Q defines six points and three landmarks as references for determination of prolapse stage and of the compartments affected. **Figure 5** below provides definitions and a pictorial expression of these points and landmarks [3].



Point	Description	Range of Values
Aa	Anterior vaginal wall 3 cm proximal to the hymen	-3 cm to +3 cm
Ba	Most distal position of the remaining upper anterior vaginal wall	-3 cm to +tvl
C	Most distal edge of cervix or vaginal cuff scar	
D	Posterior fornix (N/A if post-hysterectomy)	
Ap	Posterior vaginal wall 3 cm proximal to the hymen	-3 cm to +3 cm
Bp	Most distal position of the remaining upper posterior vaginal wall	-3 cm to + tvl

Genital hiatus (gh) – Measured from middle of external urethral meatus to posterior midline hymen
Perineal body (pb) – Measured from posterior margin of gh to middle of anal opening
Total vaginal length (tvl) – Depth of vagina when point D or C is reduced to normal position

Figure 5 – *POP-Q Points and Landmarks.* *This image is a pictorial representation of the POP-Q reference points and landmarks and includes definitions of each point and ranges of values.*

Utilizing these points, staging is determined by quantitative measurement of the location of the leading edge of prolapse as it relates to the location of the hymen as described in **Figure 6** [3].

POP-Q Staging Criteria	
Stage 0	Aa, Ap, Ba, Bp = -3 cm and C or D ≤ – (tvl – 2) cm
Stage I	Stage 0 criteria not met and leading edge < -1 cm
Stage II	Leading edge ≥ -1 cm but ≤ +1 cm
Stage III	Leading edge > +1 cm but < + (tvl – 2) cm
Stage IV	Leading edge ≥ + (tvl – 2) cm

Figure 6 – POP-Q Staging Criteria. *This table defines the stages of prolapse per POP-Q. Measurements are made of the leading edge of prolapse relative to the hymen (i.e., negative values lie above the hymen, zero values are at the hymen, and positive numbers are below the hymen).*

B. Prevalence

POP affects women of all ages; however, it more common in older women. The prevalence of POP increases with age, with a peak of five percent in women between the ages of 60-69. On physical

examination, some degree of prolapse of any type is present in 41% to 50% of women. The number of women who have POP is expected to increase by 46%, to 4.9 million, by 2050 [4].

C. Risk Factors

Established risk factors for POP include previous vaginal delivery, advanced age, and high body mass index (BMI). Additional risk factors include increased intrabdominal pressure (chronic cough, constipation, repeated heavy lifting), family history of POP, race and/or ethnicity (white/Hispanic), connective-tissue disorders, and previous hysterectomy or prolapse surgery [4]. Often, POP coexists with other pelvic floor disorders such as stress urinary incontinence (SUI), overactive bladder, and fecal incontinence [5].

D. Treatment

Most pelvic organ prolapse is asymptomatic [4]. The extent of treatment will depend on the type and stage of prolapse, patient age, and the type and severity of symptoms. Symptoms can be varied, and may include sensation of bulge, discomfort/pain, incontinence, and dyspareunia.

Symptomatic POP can be managed conservatively with pelvic floor exercises or by using pessaries, or it can be repaired surgically. Surgical repair of prolapse can be performed transabdominally (sacrocolpopexy) or transvaginally and may address one or more compartments in the vagina, depending on which areas are affected (anterior, posterior, and/or apical). In this executive summary, we will focus specifically on transvaginal surgical repair of anterior vaginal wall prolapse. This type of repair is used to treat cystocele, which is when the bladder prolapses into the vagina, and may also include an apical prolapse repair, which is when the top of the vagina drops from its correct anatomic position.

In general, transvaginal repair of prolapse may be augmented with mesh or may be performed by tissue plication and suture only (*i.e.*, native tissue repair). Surgical mesh for POP repair are pre-configured to match the anatomical defect they are designed to correct or may be cut to the needs of the surgeon in each case. Mesh placed via an abdominal procedure to repair prolapse is typically done with stand-alone mesh products, while prolapse repairs completed transvaginally may be completed with either stand-alone mesh or mesh kits (includes mesh and instrumentation to aid insertion and/or placement).

In **Section V** of this executive summary, we discuss the available safety and effectiveness information for transvaginal repair of the anterior compartment using both surgical mesh and native tissue repair.

E. Professional Society Positions

The American Urogynecologic Society (AUGS) has published several position statements that pertain to use of surgical mesh placed transvaginally in the anterior vaginal compartment as follows:

- American Urogynecologic Society Best Practice Statement: Evaluation and Counseling of Patients With Pelvic Organ Prolapse (published September/October 2017) [6]

  Regarding surgical management of POP, this best practice statement recommends “Patients may have strong preferences when it comes to use of graft, and this should be discussed. If synthetic mesh is considered, the 2011 FDA safety communication on transvaginal mesh should

be discussed...The choices of procedures provide optional use of native tissue and/or grafts, retention or removal of the uterus, and vaginal or abdominal (open, laparoscopic, and robotic-assisted) approaches. Surgeons offering various surgical treatments should be aware of the data on efficacy and complications of those procedures and offer these data to the patient during counseling."

- Position Statement on Restriction of Surgical Options for Pelvic Floor Disorders (published March 2013) [7]

  In this statement, AUGS states that in certain cases, transvaginal mesh for POP repair may be the most appropriate surgical option, particularly for women with recurrent prolapse after a non-mesh repair, patients for whom an abdominal surgical approach may pose additional and/or more significant surgical risks, and/or women with advanced prolapse. AUGS also states the importance of informed decision making by the physician and patient and the need for these procedures to be done by appropriately trained and credentialed physicians.

In April 2017, AUGS and the American College of Obstetricians and Gynecologists (ACOG) published a joint practice bulletin titled "Pelvic Organ Prolapse"[8]. Specifically, regarding anterior repair with synthetic mesh, the committee opinion states "Polypropylene mesh augmentation of anterior vaginal wall prolapse repair improves anatomic and some subjective outcomes but does not affect reoperation rates for recurrent prolapse and is associated with a higher rate of complications compared with native tissue vaginal prolapse repair. Polypropylene mesh grafts placed through anterior vaginal wall incisions improve subjective outcomes and the anatomic success rates for repair of anterior vaginal wall defects compared with native tissue repair. However, vaginally placed polypropylene mesh is associated with longer operating times and greater blood loss compared with native tissue anterior repair. The use of vaginally placed polypropylene mesh does not decrease the chance of having a repeat surgery for POP and may lead to surgeries to correct mesh-related complications. Pelvic organ prolapse vaginal mesh repair should be limited to high-risk individuals in whom the benefit of mesh placement may justify the risk, such as individuals with recurrent prolapse (particularly of the anterior or apical compartments) or with medical comorbidities that preclude more invasive and lengthier open and endoscopic procedures. Before placement of synthetic mesh grafts in the anterior vaginal wall, patients should provide their informed consent after reviewing the benefits and risks of the procedure and discussing alternative repairs."

Also in April 2017, AUGS and ACOG issued a joint committee opinion titled "Management of Mesh and Graft Complications in Gynecologic Surgery."[9] The committee opinion states that "Approaches to management of mesh-related complications in pelvic floor surgery include observation, physical therapy, medications, and surgery. Obstetrician–gynecologists should counsel women who are considering surgical revision or removal of mesh about the complex exchanges that can occur between positive and adverse pelvic floor functions across each additional procedure starting with the device implant. Detailed counseling regarding the risks and benefits of mesh revision or removal surgery is essential and can be conducted most thoroughly by a clinician who has experience performing these procedures." Regarding mesh removal in asymptomatic patients, AUGS and ACOG state "For women who are not symptomatic, there is no role for intervention. Indeed, the removal of the mesh is more likely to cause adverse symptoms than to prevent future problems. Mesh removal surgery should not be performed unless there is a specific therapeutic indication."

F. Professional Society Guidelines Regarding Training

In July/August 2012, AUGS issued privileging guidelines for physicians who placed mesh transvaginally to treat POP titled "Guidelines for Providing Privileges and Credentials to Physicians for Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse"[10]. The privileging guidelines state that "Placement of transvaginal mesh for pelvic organ prolapse should only be performed by surgeons who are Board certified or Board eligible in Obstetrics and Gynecology or Urology who also have requisite knowledge, surgical skills, and experience in reconstructive pelvic surgery. An internal audit of the surgical experience at the local institution or via statewide or national registry is also recommended to maintain quality after implementation of this surgical procedure." The guidelines provide specific recommendations for physicians who wish to begin performing transvaginal repair or POP, as well as those who already have privileges. The recommendations include documenting continuing medical education and case load with mesh repair, demonstrating experience and privileging with non-mesh repair, and the need for proctored cases when adopting new devices/technology.

III. Device Description

Surgical mesh intended for POP repair consists of a thin sheet or net of material intended to provide mechanical support in surgical repairs. Surgical mesh is available either in a non-configured form (sheet) or a pre-configured form with leg assemblies to facilitate placement of the mesh. The former type is often available in a variety of sizes to be trimmed and sutured by the surgeon to meet an individual patient's needs.

Surgical mesh materials can be divided into four general categories:

- non-absorbable synthetic (*e.g.*, polypropylene or polyester),
- absorbable synthetic (*e.g.*, poly(lactic-co-glycolic acid) or poly(caprolactone)),
- biologic (*e.g.*, acellular collagen derived from bovine or porcine sources), and
- composite (*i.e.*, a combination of any of the previous three categories).

Surgical mesh made from synthetic materials are woven from either monofilament or multifilament fibers that create a porous architecture. In addition to the fiber type and weave, other factors such as the thickness of the fibers, the density and strength of the material, the implantation technique, and the biological and physical responses of the surrounding tissue influence the performance of the mesh [11].

Based on these characteristics, non-absorbable synthetic meshes are classified with respect to their pore size and filamentous nature in four subtypes. Type I (Amid classification [12]) mesh are composed of monofilament fibers that are woven into a macroporous (>75 μm) architecture. The design of these types of mesh products is intended to promote better integration into the host tissue, as the larger pores allow for tissue to grow in and around the mesh [11]. The currently marketed synthetic surgical mesh devices for anterior repair of POP, the Boston Scientific Uphold LITE and the Coloplast Restorelle DirectFix Anterior, are Type I mesh.

Surgical mesh made from biologic materials are derived from human, bovine, and porcine tissue that has been decellularized to leave a collagen matrix. This structure is intended to act as a framework that supports remodeling and new collagen deposition. The characteristics of each material are different and dependent on the tissue source and the specific methods used to remove the cells and sterilize the graft. In vivo, these devices are exposed to various enzymes that degrade them over time. The collagen

matrix can be chemically cross-linked to prolong degradation. Non-cross-linked mesh is typically degraded in 2 to 3 months, whereas the cross-linked material can last several years [13]. However, degradation time varies by device. The currently marketed biologic surgical mesh device for anterior repair of POP, the Boston Scientific Xenform, is made of non-cross-linked fetal bovine tissue.

IV. Regulatory History

A. FDA Review of Surgical Mesh Indicated for POP Through the 510(k) Pathway

Surgical mesh is a pre-amendments device which was classified into Class II (21 CFR 878.3300) in 1988. Since the 1950s, surgical mesh has been used to repair abdominal hernias. In the 1970s, gynecologists began using surgical mesh indicated for hernia repair for abdominal repair of POP, and in the 1990s, gynecologists began using surgical mesh for transvaginal POP repair. To do so, surgeons would cut the mesh to the desired shape for POP repair and then place the mesh through a corresponding incision. Over time, manufacturers responded to this clinical practice by developing mesh products specifically designed for POP repair.

In 1996, the Surgical Fabrics (ProteGen Sling) device manufactured by Boston Scientific Corporation became the first surgical mesh cleared via the 510(k) pathway for vaginal POP repair. In 2002, Gynemesh® PS, manufactured by Ethicon/Gynecare, became the first pre-configured surgical mesh product cleared for POP repair. Surgical mesh products then evolved into "kits" that included tools to aid in the delivery or insertion of the mesh. The first kits for POP repair, the AMS Apogee™ System and the AMS Perigee™ System, both manufactured by American Medical Systems, Inc., were cleared in 2004. During the premarket notification review process, original clinical studies were not provided to support clearance of surgical mesh indicated for treatment of POP. Attempts to establish clinical safety and effectiveness were undertaken later by the clinical community with clinical trials, published studies, and systematic reviews or meta-analyses. Some of this published literature was incorporated into later 510(k) submissions to support future market clearances. Between 2002 and 2013, the FDA cleared over 100 510(k) submissions for surgical mesh with a transvaginal POP repair indication.

B. 2008 MAUDE Database Search and Public Health Notification

From 2005 – 2008, the FDA reviewed information regarding the safety of urogynecologic surgical mesh used to repair any type of POP or SUI. This information came from (1) postmarket surveillance of medical device reports (MDRs), (2) concerns raised by the clinical community and citizens, and (3) the published literature. This included an article published in 2006 that described new types of adverse events associated with mesh used for urogynecologic indications [14]. A 2008 search of the MAUDE database indicated that more than 1000 MDRs had been received for the 2005-2007 timeframe. The reported adverse events related to use of surgical mesh for POP repair included mesh erosion, infection, pain, dyspareunia, vaginal scarring, urinary retention or urinary incontinence, and recurrence of POP. As a result of the large number of adverse events received, in October 2008, the FDA issued a Public Health Notification (PHN) informing clinicians and their patients of these findings, with recommendations on how to mitigate risks and how to counsel patients [15].

C. 2011 Safety Communication and White Paper

In January 2011, to follow up on its 2008 review, the FDA completed another search of the MAUDE database for the 2008-2010 timeframe. This new search identified an additional 2874 MDRs for

urogynecologic surgical mesh, with slightly more than half associated with POP repairs of any type and the remaining MDRs associated with SUI repairs. In addition, the FDA systematically evaluated the peer-reviewed scientific literature to revisit the fundamental question of the safety and effectiveness of surgical mesh for urogynecologic indications.

On July 13, 2011, based on the 2008-2010 MAUDE database search and the FDA systematic literature review, the FDA issued a Safety Communication titled *"UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse"* to inform the medical community and patients that:

(1) serious complications associated with surgical mesh for vaginal repair of POP are not rare (a change from what was stated in the 2008 *PHN*), and

(2) it is not clear that transvaginal POP repair with mesh is more effective than traditional non-mesh repair.

The Safety Communication also provided a list of recommendations for health care providers and patients to consider before and after transvaginal POP repair with mesh [16].

Also on July 13, 2011, the FDA issued a white paper titled "*Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse.*" The purpose of the white paper was to advise the public and the medical community of complications related to transvaginal POP repair with mesh [17].

D. 2011 Panel Meeting

In September 2011, the FDA convened the Panel to discuss the safety and effectiveness of surgical mesh used to treat POP and SUI [18].

The Panel discussed the serious adverse events associated with use of surgical mesh for transvaginal POP repair. The Panel consensus was that the safety of surgical mesh for transvaginal POP repair had not been well established and that, depending on the repair compartment, transvaginal placement of surgical mesh for POP repair may not be more effective than native tissue repair. As such, the Panel concluded that the risk/benefit profile of surgical mesh for transvaginal POP repair was not well established and that these devices should be reclassified from class II (low- to moderate-risk devices) to class III (high-risk devices). The Panel also recommended issuance of postmarket surveillance study orders to collect safety and effectiveness information for these devices.

E. Postmarket Surveillance Studies

In January 2012, the FDA ordered manufacturers of urogynecologic surgical mesh devices to conduct postmarket surveillance studies ("522 studies") to address specific safety and effectiveness concerns related to surgical mesh used for transvaginal repair of POP. This order was based on the FDA's evaluation of the published literature, analysis of adverse events reported to the FDA, and feedback from the 2011 Panel meeting. In total, the FDA issued 131 postmarket study orders to 34 manufacturers of surgical mesh for transvaginal repair of POP. The FDA will use the results of the 522 studies to evaluate the safety and effectiveness of individual surgical mesh devices placed in the anterior vaginal compartment to treat POP and determine if the benefit/risk profile of each device supports continued marketing.

The 522 orders required manufacturers to answer public health questions regarding the safety and effectiveness of mesh placed transvaginally to treat POP. The 522 orders requested that manufacturers conduct a randomized controlled study or parallel cohort study comparing their device to native tissue repair. The requested effectiveness endpoints included an assessment of anatomic success, subjective success, and retreatment for prolapse. The requested safety endpoints included all device and procedure related adverse events, as well as the rate of individual adverse events of interest (mesh erosion, de novo urinary dysfunction, de novo dyspareunia, etc.). The FDA requested evaluation of the safety and effectiveness endpoints at six-month intervals out to 24 months and at 36 months.

Most manufacturers elected to stop marketing surgical mesh for transvaginal repair of pelvic organ prolapse after receiving their 522 orders. Currently, there are four ongoing 522 studies for five surgical mesh devices placed transvaginally to treat POP as follows:

- Boston Scientific Uphold LITE (anterior/apical prolapse)
- Boston Scientific Xenform (anterior/apical prolapse)
- Coloplast Restorelle DirectFix Anterior (anterior/apical prolapse) and Restorelle DirectFix Posterior (posterior/apical prolapse)
- Acell Matristem Pelvic Floor Repair Matrix (total prolapse)

Please note that although the 522 studies for the Coloplast Restorelle DirectFix Posterior and Acell Matristem Pelvic Floor Repair Matrix are ongoing, these devices are no longer marketed.

F. Proposed and Final Reclassification Orders

In April 2014, the FDA issued two proposed orders for surgical mesh for transvaginal POP repair that put forth changes in the regulatory classification and premarket requirements to address the risks associated with these devices. The FDA proposed reclassifying surgical mesh for POP repair from class II to class III (79 FR 24634)[19]. The FDA also proposed requiring the filing of a premarket approval application (PMA) (79 FR 24642)[20].

In January 2016, the FDA issued two final orders that: (1) reclassified surgical mesh for transvaginal pelvic organ prolapse (POP) repair from class II to class III (81 FR 353)[21] and (2) required the filing of a PMA for surgical mesh for transvaginal POP repair (81 FR 363)[22]. As stated in this final order, a PMA for surgical mesh for transvaginal POP repair was required to be filed on or before July 5, 2018, for any preamendments Class III devices that were in commercial distribution before May 28, 1976, or that had been found to be substantially equivalent to such a device on or before July 5, 2018. If a PMA was not filed by July 5, 2018, then the device would be deemed adulterated under section 510(f) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and could no longer be marketed in the United States. Currently, three surgical mesh devices indicated for anterior transvaginal POP repair are marketed in the United States – Boston Scientific Uphold LITE, Boston Scientific Xenform, and Coloplast Restorelle DirectFix Anterior.

G. Regulatory Actions Outside of the United States

In May 2014, Health Canada issued an updated notice to hospitals regarding the use of mesh placed transvaginally to treat POP and SUI. Regarding mesh placed transvaginally to treat POP, Health Canada stated that these procedures have a higher risk of complications compared to native tissue repair and mesh placed abdominally, complications associated with these procedures may require additional

surgery to repair which may not fully correct the complications, and surgeons placing these devices should have adequate training and be familiar with the device labeling [23].

In December 2017, the Australian Therapeutic Goods Administration (TGA) stated that "benefits of using transvaginal mesh products in the treatment of pelvic organ prolapse do not outweigh the risks these products pose to patients." TGA made this conclusion based on its review of the published literature. As a result, Australia de-registered (removed from the market) all urogynecologic surgical mesh products due to these safety concerns [24].

In 2018, the United Kingdom and Ireland placed a pause on the use of all surgical mesh placed transvaginally for POP and SUI. This pause was a result of concerns raised by patient advocacy groups regarding the safety of these devices. Per the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom, this decision was not based on new scientific or clinical evidence [25]. Also, in 2018, Scotland stopped all transvaginal mesh procedures until a new "restricted use protocol" could be developed and implemented to ensure that procedures can only be carried out in limited circumstances [26].

V. FDA Review of Published Literature

The FDA reviewed the published literature for safety and effectiveness outcomes related to mesh placed in the anterior vaginal compartment to treat POP. **Appendix I** describes the literature review methodology, as well as its strengths and limitations. The FDA literature review covered the period from January 1, 2008 to November 1, 2018. This date range was selected to align with the FDA 510(k) clearance of surgical mesh kits specifically designed for transvaginal repair of POP in the anterior vaginal compartment, allowing for sufficient time following 510(k) clearance and for the completion and publication of clinical studies. The search was limited to studies that evaluated surgical mesh used for transvaginal repair of anterior and/or apical POP with at least 12-month safety and effectiveness outcomes on at least 25 patients. The types of studies included randomized controlled trials, prospective cohort studies of currently marketed devices for anterior repair of POP (Boston Scientific Uphold or Uphold LITE, Boston Scientific Xenform, and Coloplast Restorelle or Coloplast Restorelle DirectFix Anterior), large database or registry studies, meta-analyses, and Markov analyses.

The FDA notes that the Boston Scientific Uphold and Uphold LITE are different products, with the Uphold having a higher mesh density than the Uphold LITE. Uphold is no longer marketed. Restorelle is the broader Coloplast product line of urogynecologic surgical mesh. DirectFix Anterior is the only Restorelle product that is currently marketed for transvaginal repair of POP in the anterior compartment. The remaining Restorelle products that are currently marketed are indicated for abdominal repair of POP; however, some Restorelle products were previously indicated for transvaginal repair of POP.

Please note that the FDA literature review focuses on use of mesh or native tissue repair for primary repair of POP in the anterior vaginal compartment. There are limited data in the literature regarding use of mesh or native tissue repair to treat recurrent prolapse. The devices currently on the market are currently used for both primary and secondary repair.

Appendix II provides tables summarizing the literature review; individual tables are referenced along with the relevant discussion below.

As noted in the introduction, the FDA is seeking panel input on assessing the effectiveness, safety, and benefit/risk of mesh placed transvaginally in the anterior vaginal compartment. Regarding effectiveness, the FDA requests Panel input on whether mesh should be more effective than native tissue repair, at what timepoint, and if both anatomic and subjective outcomes should be used to assess effectiveness. Regarding safety, the FDA requests Panel input on the types of adverse events that should be used to evaluate safety and how those adverse events should be assessed, whether the adverse event profile of mesh should be similar to native tissue repair, and at what timepoints a safety comparison to native tissue repair should be completed. For both safety and effectiveness, the FDA asks the Panel to weigh in on any special considerations related to the mesh material. The FDA is also seeking Panel recommendation on identifying the appropriate patient population and physician training needed for these devices.

Please note that the FDA is not asking the Panel to determine the safety and effectiveness of specific devices or surgical mesh placed transvaginally in the anterior vaginal compartment collectively. The FDA literature review draws general conclusions regarding the safety and effectiveness of surgical mesh placed transvaginally in the anterior vaginal compartment. However, the FDA is providing this information to give context around how the safety and effectiveness of surgical mesh placed transvaginally in the anterior vaginal compartment are typically assessed and the key considerations that affect these outcomes. The FDA intends to use the recommendations from the Panel to complete its review of the 522 studies for the Boston Scientific Uphold LITE, Boston Scientific Xenform, and Coloplast Restorelle DirectFix Anterior.

A. Effectiveness of Mesh Placed in the Anterior Vaginal Compartment to Treat POP

The effectiveness of POP treatments can be assessed objectively or subjectively. Objective assessments include POP-Q, as described in **Section II** of this executive summary, or other anatomic evaluations for prolapse stage. Subjective outcomes are patient reported outcomes that include an assessment of patient symptoms related to prolapse. Retreatment for recurrent POP is another outcome of interest to determine the success of a POP repair.

The FDA believes that a combination of objective and subjective outcomes, as well as an assessment of retreatment for recurrent POP, is needed to adequately evaluate the effectiveness of surgical mesh placed in the anterior vaginal compartment against native tissue repair. Objective outcomes provide a quantitative assessment of effectiveness; however, because patients undergo surgical repair of POP to improve quality of life, subjective or patient reported outcomes are also critical in evaluating effectiveness. Subjective outcomes may be challenging to evaluate because patients vary in their assessment of a meaningful improvement and what is considered a bothersome symptom. In addition, an individual patient's assessment may be affected by her sexual activity level and/or blinding to her treatment type (mesh or native tissue repair) within a clinical study.

1. Overview of Effectiveness Results

Meta-analyses

Table A1 describes the study designs of the meta-analyses that were reviewed, and **Table A2** summarizes the results of these meta-analyses. Based on these meta-analyses, effectiveness outcomes of resurgery for POP and objective cure were generally more favorable for surgical mesh patients compared with native tissue repair patients. Subjective outcomes such as satisfaction, quality of life

variables, and sexual function were generally similar between surgical mesh and native tissue repair. When mesh erosion or exposure was included in the resurgery outcome along with POP recurrence, then the native tissue repair group had more favorable outcomes in two meta-analyses, as patients are not at risk for mesh erosion/exposure after native tissue repair procedures [27, 28].

Databases Studies

Table A4 describes the study designs of the 14 database studies that were reviewed, and **Table A5** summarizes the main results from these large database studies. Large databases, such as the Medicare database, provided real world evidence in large samples of women. Although claims data generally do not include patient reported outcomes, a Swedish registry also reported results for the subjective outcomes of patient reported cure, satisfaction, improvement, and feeling of protrusion [29]. This study found more favorable subjective outcomes for the mesh group compared to native tissue repair. The rate of reoperation/resurgery for POP mesh complications was consistently around 5-6% between 1-5 years follow-up, with the exception of one study that reported a resurgery rate closer to 10% [30]. A study using MarketScan data demonstrated a greater five year cumulative risk for mesh patients compared to native tissue repair for any repeat surgery (POP or mesh complications), but similar risk for surgery for recurrent prolapse [30]. Of seven studies that compared resurgery or reintervention rates for mesh versus native tissue repair, five reported more favorable results for the native tissue repair group [30-34], one reported more favorable results for the mesh group [35], and one reported similar rates between groups [36]. Therefore, there were mixed effectiveness results reported by the database studies. Overall, mesh patients tended to have a higher risk of resurgery for POP or mesh complications than native tissue repair subjects.

Randomized Controlled Trials (RCT)

Table A6 describes the study designs of the 30 RCTs that were reviewed. The results of RCTs which randomized patients to mesh versus native tissue repair are shown in **Table A7** (one year follow up), **Table A8** (two year follow up), and **Table A9** (three year follow up). Regarding objective outcomes from RCTs, all studies reported either statistically significant favorable results for the mesh group compared to the native tissue repair group, or no statistically significant differences between the two groups. The largest RCT, the NIH-funded PROSPECT trial performed in the UK, found no statistically significant differences in POP-Q stage or reoperation rates at one year for either synthetic or biologic mesh when compared to native tissue repair [37, 38]. Regarding subjective outcomes, most studies reported no statistical significance between group differences. The RCTs generally reported higher effectiveness for mesh patients for objective outcomes but similar effectiveness for mesh and native tissue repair when comparing subjective patient reported outcomes for 1-3 years of follow-up.

Prospective Cohort Studies

The prospective cohort studies are summarized in **Table A10**. There are seven prospective cohort studies (represented by eight articles) which evaluated a currently marketed mesh product (or a previous iteration of that product). All studies included one year of follow-up. Four studies specified Uphold or Uphold LITE [39-43], two studies specified Restorelle mesh [44, 45], and one study specified Xenform. The Uphold studies reported high rates of anatomic cure based on POP-Q score (94-97%) and composite cure based on POP-Q plus subjective symptoms (74-97%); reoperation rates were between 1-7%. Only one Uphold study compared mesh to a native tissue repair cohort and reported similar cure rates between groups [39]. The two Restorelle studies also reported high rates of cure based on POP-Q

score (92-95%), reintervention (8.5%), and quality of life improvement. The Xenform study demonstrated improvement in objective and subjective outcomes at 12 months [46]. Six of the eight articles reported funding or disclosed a relationship with Boston Scientific [39-43].

Markov Analysis

Dieter (2015) performed a Markov analysis using published studies and meta-analyses, to compute the theoretical probability of reoperation for recurrent prolapse or mesh exposure/erosion, using published rates of reoperation. The model predicted a 30 to 70% probability (based on varying assumptions) that mesh would result in a greater number of operations for recurrent prolapse repair or mesh erosion/exposure over two years of follow-up than native tissue repair [47]. This conclusion is consistent with other evidence reviewed.

Summary

Overall, between 1-3 years of follow-up, published literature indicates mesh may have some advantage over native tissue repair for anatomic POP evaluation and reoperation for recurrent POP only; however, the subjective outcomes are generally similar between groups except for one large database study [29]. Most articles reported an improvement in quality of life and prolapse symptoms for both mesh and non-mesh groups post procedure. Additionally, when considering reoperation for either prolapse recurrence or mesh erosion/exposure, mesh patients had greater odds of reoperation.

2. Effectiveness Results by Timepoint

No major differences were noted by timepoint for mesh versus native tissue repairs. The database study with the longest follow-up, which presented five year results for apical repair patients in the Truven MarketScan and Medicare databases, reported no significant differences in resurgery for recurrent prolapse between mesh and native tissue repair at five years [32]. However, a different study, also using MarketScan data, reported that patients receiving anterior repair had higher risk of reoperation due to mesh complications but the same risk of reoperation due to recurrent prolapse, compared with native tissue repair [30]. Therefore, these data suggest that mesh outcomes are similar to those of native tissue repair out to five years regarding prolapse recurrence and resurgery, but mesh complications lead to additional reoperations for mesh patients. These RCT results are presented in **Tables A7, A8, and A9**, by one, two, or three years of follow-up, respectively.

Reoperations appear to occur throughout at least three years post operation. The New York SPARCS dataset showed that the reintervention rate increased from 4.0% at one year to 6.3% at three years follow-up, and Kaplan Meier curves indicated that reinterventions occurred throughout the three year period; [36] therefore, reinterventions were not limited to the first year.

Due to limited data with longer follow-up, conclusions are fairly limited past three years of follow-up. Also, most articles did not present rates over time, so it is difficult to draw conclusions about when reoperations may occur and if there are differences between mesh and native tissue repair with regards to the timing of reoperation. However, evidence suggests that reintervention for recurrent POP occurs through at least three years, and studies with the longest period of follow-up do not show significant differences between mesh and native tissue repair patients at five years.

3. Effectiveness Results by Mesh Material

The Cochrane review and meta-analysis by Maher (2017) for anterior repair reported that there is a minimal advantage for biological graft or for polypropylene mesh compared to native tissue repair, based on outcomes of awareness of prolapse, repeat surgery for prolapse, or recurrent prolapse. However, the risk ratios compared to native tissue repair were more favorable for polypropylene than biological graft, indicating that synthetic mesh may have better effectiveness as summarized in **Table A2**. The authors reported that there was little data available for absorbable mesh (*e.g.*, biological graft) [27].

Glazener (2017) conducted a large RCT to compare synthetic mesh versus native tissue repair and biologic graft versus native tissue repair. The authors reported no statistically significant between group differences (synthetic/biologic mesh versus native tissue repair) in POP-Q outcomes, reoperation for POP, or quality of life outcomes, at either one or two year follow-up, and concluded that neither synthetic mesh nor biologic graft improved effectiveness outcomes compared to native tissue repair [37].

Farthmann (2013) reported a higher rate of anterior POP recurrence at one year for patients who received partially absorbable mesh (polypropylene with an absorbable coating of polyglycolic acid and caprolactone) compared to patients who received polypropylene mesh [48].

Goldstein (2010) conducted a prospective cohort study of 45 subjects demonstrating improvement in objective and subjective outcomes at 12 months when using Xenform [46].

It is difficult to draw definitive conclusions regarding how effectiveness may vary by material, although there is some evidence to suggest that polypropylene mesh may have more of an advantage over native tissue repair compared to biological graft.

4. Effectiveness Results by Brand

Not all articles specified mesh brand, and there was no evidence to suggest that any certain brand was more or less effective than the others. The vast majority of articles that specified mesh brand noted brands that are not available in the U.S. or off the market, such as Prolift, Apogee, Perigee, Avaulta, and Nazca. Other articles specified the use of mesh made of polypropylene, but this could include multiple brands of mesh, such as Gynemesh - which is not pre-cut into a specific shape for POP repair (unlike Uphold LITE and Restorelle DirectFix Anterior which are pre-configured). There were few articles that focused on one of the three brands currently on the market in the United States (Uphold LITE, Xenform, Restorelle DirectFix Anterior). **Table A10** describes these prospective cohort studies. None of the studies had more than one year of follow-up.

B. Safety of Mesh Placed in the Anterior Vaginal Compartment to Treat POP

The FDA believes that the risk profile of surgical mesh placed in the anterior vaginal compartment is greater than that of native tissue repair. This is because mesh erosion/exposure, which can be serious and potentially debilitating, is associated only with surgical mesh and not native tissue repair. Management of mesh erosion may not be uncomplicated, may require multiple additional surgeries to address, and may remain unresolved despite treatment. Further, identification and treatment of mesh erosion may depend upon whether or not a patient is sexually active.

1. Overview of Safety Results

The FDA literature review focused on safety comparisons between mesh and native tissue repair patients. The safety results are presented by study in **Tables A3-5 and A7-10**.

2. Mesh Erosion/Exposure

Please note that some authors refer to mesh erosion and exposure synonymously, while others may make a distinction between the two. This review uses the term used originally by each author, when referring to that study.

In the meta-analyses reviewed, the rates of mesh exposure, erosion, and/or extrusion were generally between 3-15% in the first 3-5 years postoperation. No between-group comparisons with native tissue repair patients were generally available unless study inclusion criteria allowed concomitant mesh sling for SUI; therefore, this type of mesh-related complication is considered a safety concern for mesh patients only (exceptions are noted in the **Tables A3-5 and A7-10)**.

The highest level of evidence from the Cochrane reviews indicated that the rate of mesh erosion for anterior repair was 11.3%, for apical repair was 18% (with 9.5% requiring surgical intervention), and for anterior/apical/posterior combined was 12% (with 8% requiring surgical intervention) [27, 49]. Of note, the enrollment of one RCT referred to as the "Vaginal Mesh for Prolapse (VAMP)" trial was halted prematurely by its Data Safety Monitoring Board, due to the high rate (15.6%) of mesh exposure which had exceeded the predetermined stopping criteria of 15% [50-52]. This trial used the Prolift polypropylene mesh kit.

There was some evidence that mesh exposure/erosion appears to occur most frequently in the first three months to one year post operatively, [53-55] although exposures can occur through at least three years of follow-up. In one RCT, the mesh exposure rate after surgery with polypropylene or partially absorbable mesh was fairly steady over time (7.4% present at three month follow-up, 6.4% present at one year, and 5.4% present at three years; 14.6% cumulative rate over three years). The authors note, however, that there were exposures present at three years that were not present at one year (6/27, or 22% of exposures), and emphasized that most of the surgeries for exposure occurred after one year [48]. Additionally, the VAMP trial reported that 15.6% of patients experienced mesh exposure within one year, and there was one additional asymptomatic mesh exposure identified at the three year visit [50]. Therefore, erosions/exposures can occur more than one year after surgery, through three years; no evidence was identified past three years.

There may be certain patient characteristics that are risk factors for mesh exposure/erosion. Deng 2016 performed a meta-analysis of RCT, prospective, and retrospective studies to assess possible risk factors for mesh erosion after pelvic floor reconstruction surgery. The overall prevalence of mesh erosion was 7.43%. Regarding risk and protective factors, the authors concluded the following: "Statistically significant differences in mesh erosion after female pelvic floor reconstruction were found in older vs younger patients ([odds ratio] OR 0.96, 95% CI 0.94–0.98), more parities vs less parities (OR 1.27, 95% CI 1.07–1.51), the presence of premenopausal/oestrogen replacement therapy (ERT) (OR 1.36, 95% CI 1.03–1.79), diabetes mellitus (OR 1.87, 95% CI 1.35–2.57), smoking (OR 2.35, 95% CI 1.80–3.08), concomitant pelvic organ prolapse (POP) surgery (OR 0.37, 95% CI 0.16–0.84), concomitant hysterectomy (OR 1.46, 95% CI 1.03–2.07), preservation of the uterus at surgery (OR 0.22, 95% CI 0.08–

0.63), and surgery performed by senior vs junior surgeons (OR 0.42, 95% CI 0.30–0.58).” No statistically significant association was found for BMI, menopause, hypertension, POP-Q stage ≥III vs <III, previous pelvic surgery, previous hysterectomy, concomitant SUI surgery, or postoperative sexual activity [56].

Nguyen (2012) reported that the rate of resurgery for mesh exposure varied significantly by compartment; the rates for anterior, posterior, and apical repair were 6%, 2%, and 2%, respectively.

Erosions and exposures can be managed conservatively (estrogen cream, mesh removal in office) or may sometimes require surgical mesh removal in the operating room. Treatment decisions may be based on variables such as level of bother and level of sexual activity, although this was not commonly reported. Nieminen (2010) reported that of 20 patients with mesh erosion, 6/20 (30%) were treated with topical estrogen and 14/20 (70%) were treated with closure of the epithelium and partial resection of the mesh; no patients underwent removal of the mesh. A total of eight patients returned to the operating room because of mesh exposure, and the others were treated on an outpatient basis [57].

One RCT testing the effect of preoperative vaginal estrogen (0.5g promestriene cream transvaginally twice a week for six weeks before surgery) reported that the rate of mesh exposure one year after implantation of Avaulta Biosynthetic mesh was similar in the estrogen group (16.1%) compared to the non-estrogen group (12.9%), which met statistical significance for non-inferiority (comparing no estrogen to estrogen) [58]. Other articles mentioned in the methods sections that the surgeons typically advised all patients to use topical estrogens preoperatively or postoperatively because it is believed to decrease chance of mesh exposure (*e.g.*, Vollebregt 2012 [59]).

Weidner (2013) performed a Markov analysis, and calculated that use of perioperative vaginal estrogen therapy would theoretically reduce mesh erosion rates from 7.8% to 2.0% if the efficacy of estrogen was assumed to be 50-75%. Therefore, although this study does not provide the same level of evidence as a clinical trial, it does provide some theoretical evidence that estrogen therapy may provide some benefit in reducing erosion rates [60].

Skoczylas (2013) also performed a Markov analysis comparing conservative treatment (minimal trimming of exposed mesh in the office and/or vaginal estrogen therapy) versus surgical treatment (partial or total removal of mesh in the operating room) of mesh exposure. The authors used success and complication rates of treatment of mesh exposure from the published literature to compute the theoretical probably of being healed and the resultant quality adjusted life years after treatment. The analysis found a small advantage for surgical excision over conservative treatment; however, this difference was less than the minimally important difference, which suggests that the two strategies have similar outcomes. Therefore, this study does not provide support for surgical versus conservative treatment of mesh exposure [61].

Overall, mesh erosion/exposure is a fairly common (approximately 11-18%) complication among those who receive transvaginal mesh for POP and is typically not a risk for those who receive native tissue repair unless they receive concomitant sling for SUI. Erosions may be symptomatic or asymptomatic and may be treated conservatively or may require resurgery for mesh revision or removal; however, there is limited high quality evidence regarding what treatments may be most effective in treating or preventing erosions.

3. De Novo SUI

Many studies did not differentiate between persistent SUI and de novo SUI. The Cochrane review and meta-analysis by Maher (2017) for anterior repair reported that polypropylene mesh was not associated with higher risk of de novo SUI than native tissue repair. There was also no difference for biologic graft versus native tissue repair when comparing overall SUI, but not enough evidence to compare de novo SUI. There was not enough evidence to compare absorbable mesh versus native tissue repair [27]. However, the Cochrane review of mesh for all compartment repairs (anterior, apical, and posterior) reported that there was a higher rate of SUI for mesh versus native tissue repair [28]. Among the RCTs and database studies reviewed, there were mixed results for between group differences in de novo SUI. **Tables A3-5 and A7-10** reflect either SUI or de novo SUI as presented by the authors.

4. De Novo Dyspareunia

The meta-analyses did not report any significant between group differences in dyspareunia or de novo dyspareunia. Only one RCT reported a small but statistically significant difference in de novo dyspareunia at one year (2.7% in mesh group versus 0% in native tissue repair group); [53] in the three year follow-up, which was published separately, the authors noted no new dyspareunia had been observed [54]. Other studies reported differing rates of dyspareunia, but either the differences were not statistically significant or not statistically tested. Therefore, no evidence was identified that strongly suggested a difference between mesh and native tissue repair with respect to dyspareunia.

5. Other Adverse Events

Rates of some additional events including pelvic pain, infection, and voiding dysfunction are shown in **Tables A3-5 and A7-10**. Other events such as atypical vaginal discharge, neuromuscular problems, vaginal scarring, de novo vaginal bleeding, vaginal shortening/constriction, and fistula formation were not noted in the studies reviewed. Additionally, one database study using the New York SPARCS dataset tested for de novo autoimmune disease (Chughtai 2017b) but did not find an association with mesh use [62].

6. Safety Results by Timepoint

The RCT results are presented by one, two, and three years of follow-up in **Tables A7-10**, respectively. At all three timepoints, most studies favored the native tissue repair arm with regards to safety outcomes. This conclusion is primarily driven by the mesh erosion/exposure rates for the mesh arm; however, statistically significantly higher rates of de novo dyspareunia and de novo SUI were also observed in the mesh arm.

Database studies had up to five years of follow-up. No obvious patterns emerged with regards to the timing of adverse events.

7. Safety Results by Mesh Material

The PROSPECT RCTs reported that mesh-related complications were higher in patients who received synthetic mesh (6% versus <1% in native tissue repair); comparatively, mesh complications were similar between biologic and native tissue repair (both <1%). Please note that mesh related complications in the native tissue repair group are associated with the concomitant placement of a sling for SUI [37, 38].

Natale 2009 conducted an RCT to compare Gynemesh synthetic mesh versus Pelvicol biologic graft for recurrent cystocele. Mesh erosions occurred in 6.3% of synthetic and 0% of biologic mesh patients [63].

Farthmann 2013 reported a lower rate of mesh exposure at one year for patients who received partially absorbable mesh (polypropylene with an absorbable coating of polyglycolic acid and caprolactone) compared to patients who received polypropylene mesh.

Goldstein (2010) reported no graft related erosions or pain lasting more than 30 days when using Xenform [46].

Therefore, the evidence suggests that patients who receive synthetic polypropylene mesh are at greater risk for mesh erosion than patients who receive biologic graft, partially absorbable mesh, or native tissue repair.

C. Concomitant Procedures

Concomitant procedures are not infrequently completed along with transvaginal repair of prolapse in the anterior vaginal compartment. These procedures may affect safety and effectiveness outcomes, and it may be challenging to distinguish between outcomes associated with the concomitant procedure compared to the transvaginal prolapse repair procedure.

This section will summarize the concomitant procedures typically completed during transvaginal repair of prolapse in the anterior vaginal compartment, and how they may affect safety or effectiveness outcomes of a mesh or native tissue repair in the target compartment. There was no information available in the literature about how these factors may affect patient assignment to treatment, other than brief mentions of some women preferring uterine sparing surgery to hysterectomy. The most common concomitant procedures discussed were hysterectomy and midurethral sling placement for SUI.

1. Midurethral Sling

Chughtai (2015) reported that the proportions of patients who had concomitant sling placement in the mesh and no mesh group in the NY SPARCS dataset were 20.0% and 14.4%, respectively [34]. Anger (2014) reported that among Medicare beneficiaries, 15% of prolapse repair surgeries (mesh and non-mesh) had concomitant sling placement; 48.2% of prolapse repair surgeries using mesh had concomitant sling placement [35]. Jonsson Funk et al (2013) analyzed the MarketScan database and reported that 70.6% of mesh patients and 62.4% of native tissue repair patients received a recent (within six months prior to procedure) or concurrent sling placement [30]. Therefore, it appears that concomitant (or recent) sling placement at the time of POP mesh surgery is fairly common.

Chughtai (2017) reported a higher rate of erosions with concomitant SUI sling (2.7% vs. 1.9%), and a higher rate of resurgery (5.6% vs. 4.3%). The authors suggest that this is supportive of a dose response relationship between amount of mesh used and future mesh erosions [64].

2. Hysterectomy

Jonsson Funk (2013) reported that 18.4% of mesh patients and 38.3% of the native tissue repair patients received concurrent hysterectomy [30]. Dandolu (2017) reported that 9.2% of patients receiving transvaginal mesh repair also received concomitant hysterectomy, compared with 23.5% of patients receiving native tissue repair [32]. Chughtai (2015) reported that the proportions of patients who had concomitant hysterectomy in the mesh and no mesh group were 38.5%, and 51.3%, respectively [34]. Therefore, concomitant hysterectomy is also fairly common, and perhaps more common for patients undergoing native tissue repair procedures than mesh procedures.

The meta-analysis by Deng (2016) showed that those who received a concomitant hysterectomy were 1.46 times more likely to experience mesh erosion (95% CI: 1.03-2.07) [56]. Similarly, Farthmann (2013) reported that concomitant hysterectomy was a significant risk factor for exposure (OR=3.80, 95% CI: 1.46-9.89) [48]. Forde (2017) analyzed the SPARCS dataset and reported that there was no significant difference in three year reintervention rates between those who did and did not receive concomitant hysterectomy [36].

D. Patient Characteristics

A variety of patient factors may influence safety and effectiveness outcomes for mesh and/or native tissue repair. In a clinical study setting, when comparing outcomes between these two treatments, the FDA believes it is important that key patient factors are balanced between both treatment groups.

1. Age

Studies varied in how they treated age as an inclusion/exclusion criterion; for example, some limited enrollment to those over 65 years of age (*e.g.*, Anger, 2014 [35]). Others treated age as a confounder or a variable in a propensity score model. A few studies specifically tested associations and interactions by age.

The meta-analysis by Deng (2016) showed that younger patients (younger than 60-70 years of age) were slightly less likely to develop mesh erosion (OR= 0.96, 95% CI 0.94–0.98); however, this association was no longer statistically significant in multivariable adjusted models [56]. Conversely, Farthmann (2013) reported that younger age was a statistically significant risk factor for mesh exposure (OR=0.60 per ten years, 95% CI: 0.39-0.95) [48].

Chughtai (2015) stratified analyses by age (<65 or ≥65) and did not find significant differences between age groups in rates of erosion, resurgery, or resurgery with erosion diagnosis [34]. Altman (2011) tested for interaction between mesh versus non-mesh by age (32-58, 59-64, 65-71, or 72-91) and did not find a significant interaction; there were similarly higher odds of treatment success for the mesh group across age groups [65]. Therefore, there was some mixed evidence, but no strong evidence that age affects treatment outcomes.

2. Obesity

In the meta-analysis by Deng (2016) testing risk factors for mesh erosion, the authors reported that there was no significant difference between patients with higher BMI versus lower BMI (OR=1.04, 95% CI: 0.98-1.11) [56]. Additionally, Farthmann (2013) reported that BMI was not a statistically significant

risk factor for mesh exposure in their RCT [48]. Therefore, this review did not identify evidence that obesity affects safety or effectiveness outcomes.

3. Current Level of Sexual Activity

No studies limited enrollment based on current level of sexual activity. Some studies reported rates of de novo dyspareunia using a denominator of only women who were currently sexually active. However, this review did not identify evidence that level of sexual activity affects outcomes.

4. Other

As noted previously, the meta-analysis by Deng (2016) reported multiple patient characteristics that may be risk factors for mesh erosion after pelvic floor reconstruction surgery. Notably, parity, premenopausal estrogen therapy, diabetes, and smoking were risk factors for mesh erosion [56].

E. Physician Characteristics

Similarly, a variety of physician factors may influence safety and effectiveness outcomes for mesh and/or native tissue repair. In a clinical study setting, when comparing outcomes between these two treatments, the FDA believes it is important that key physician factors are balanced between both treatment groups.

Eilber (2015) reported that there was a statistically significant difference in reoperation rates between low (1 case annually), intermediate (2 cases annually), and high volume (3 or more cases annually) surgeons after surgery using mesh. The cumulative reoperation rates at one year for low, intermediate, and high-volume providers were 6%, 2%, and 3%, respectively; however, more than half of procedures were performed by low volume providers. There was no significant difference in reoperation rates (4% for each group) between gynecologists, who performed 73% of the procedures, and urologists, who performed 26% of the procedures. The authors conclude the following: “we observed lower reoperation rates among high-volume surgeons and propose that increased surgeon experience has an influential role in outcomes of vaginal surgery with mesh.”[66]

The meta-analysis of six studies by Deng (2016) showed that patients operated upon by a senior surgeon had a significantly lower risk of mesh erosion after surgery compared to those operated upon by junior surgeons (OR 0.42, 95% CI 0.30–0.58, $p < 0.001$) [56].

Therefore, from this limited evidence, there may be better effectiveness and safety outcomes for surgeons with senior status or high-volume practices, who have more experience with mesh surgeries.

F. Literature Review Conclusions

The FDA literature review summarized the evidence regarding the benefits and risks of mesh versus native tissue repair for POP.

The Cochrane review regarding anterior repair concluded the following: “Current evidence does not support the use of mesh repair compared with native tissue repair for anterior compartment prolapse owing to increased morbidity” [27]. The Cochrane review regarding anterior, apical, and posterior repair concluded the following: “While permanent mesh has some advantages over native tissue, there are

also disadvantages in its routine use. Many transvaginal permanent meshes were withdrawn from use in 2011, and the newer, lightweight transvaginal permanent meshes still available have not been evaluated within a randomised study" [28].

The consensus of the highest quality evidence currently available from meta-analyses of RCTs and large database studies appears to suggest that the objective effectiveness of mesh as measured by recurrence or POP-Q exam may be somewhat better than native tissue repair (although some studies showed same or slightly worse outcomes than native tissue repair). However, this may not always translate to increased improvement in subjective symptoms or quality of life, and mesh and native tissue repair patients generally report similar levels of improvement postoperatively. Additionally, mesh erosion/exposure occurs at a rate of approximately 11-18% and may require surgical revision and/or removal, thus driving up the rates of reoperation for mesh patients.

Rates of other types of safety events such as urinary tract infection were not consistently reported. Most studies focused on synthetic polypropylene mesh, which appears to have a higher rate of mesh erosion than biologic graft.

Overall, use of surgical mesh in the anterior vaginal compartment does not appear to offer a consistent effectiveness benefit compared to native tissue repair, particularly when considering subjective outcomes. The risks of using mesh in the anterior vaginal compartment are greater than native tissue repair, particularly with respect to resurgery for all indications (recurrence and mesh complications).

However, these conclusions are somewhat limited by the heterogeneity of the study designs and variable definitions. This review was not able to delve into differences between mesh materials, especially newer lightweight and partially absorbable meshes. These conclusions are also limited to the time period 1-6 years after prolapse repair, with most of the relevant studies with high level of evidence included one to three years of follow-up. There were no studies identified with more than six years of patient follow-up.

VI. FDA Review of Medical Device Reports

The FDA reviewed the MDRs submitted for adverse events related to surgical mesh placed transvaginally in the anterior compartment to treat POP. The FDA requests the Panel's input on the types of adverse events that should be used to evaluate safety and how those adverse events should be assessed. The following MDR analysis is intended to provide real world evidence to complement the FDA literature review.

The FDA completed a search of the MDR database from January 2008 to October 2018 for MDRs associated with mesh placed in the anterior vaginal compartment to treat POP. This date range is consistent with the literature review and covers the full-time period of FDA regulatory actions and communications related to urogynecologic mesh, which are a significant driver in adverse event reporting. **Appendix III** includes the methods and limitations of the MAUDE database search.

The search identified a total of 11,274 MDRs, including 10,391 reports of serious injury, 806 reports of device malfunctions, and 77 reports of death.

Figure 6 depicts the number of MDRs over time. As noted previously, the FDA completed a series of regulatory actions related to mesh for transvaginal repair of prolapse in 2011 and 2012. In 2013, there

was a high of 3881 MDRs, and this increase in MDRs may be in response to those actions. Conversely, the sharp drop in MDRs after 2013 is suspected to be the result of many manufacturers electing to stop marketing their devices indicated for transvaginal repair of POP upon issuance of the 522 orders. As previously stated, only three devices currently remain on the market for anterior repair. However, the number of devices on the market does not necessarily correlate to the number of procedures.

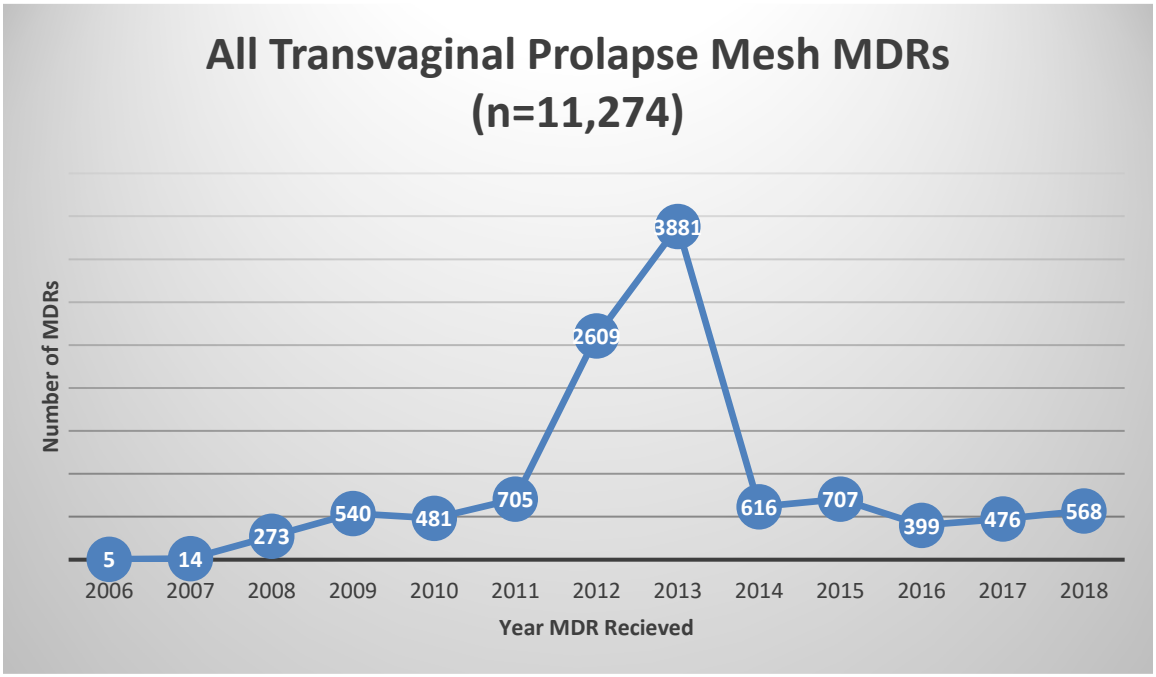


Figure 6 – ***MDRs per year from January 2008 to October 2018.***

Table 1 depicts the top ten patient problems received from January 2008 to October 2018. Please note that codes of "Other (for use when an appropriate patient code cannot be identified)" (n= 1,794), and "No Code Available" (n= 561) did not provide any insight as to a device problem and were therefore omitted from the table identifying the top patient problems. This list is not all inclusive and more than one patient problem code is often found in a single MDR.

	Patient Problem	Count
1	Pain	3717
2	Erosion/Exposure	3509
3	Infection	1794
4	Injury	1701
5	Incontinence	814
6	Scar Tissue	761
7	Bleeding	475
8	Infection, Urinary Tract	371
9	Disability	339
10	Neurological Deficit/Dysfunction	272

Table 1 – ***Top 10 patient problems for MDRs received from January 2008 to October 2018.***

The most common patient problems reported in MDRs are consistent with those observed in the published literature. The differences are in terminology; none of the top ten MDR patient problems were missing in the literature. While FDA is unable to calculate rates from the MDRs, these data provide real world evidence that adverse events associated with these devices are not rare. Erosion/exposure of the mesh is the second most commonly reported patient problem in women treated with mesh for POP.

Appendix IV provides the MDRs per year and top ten patient problems for the three marketed devices indicated for anterior repair of POP. The trend in MDRs per year and the top ten patient problems for the three marketed devices are consistent with **Figure 6** and **Table 1**.

VII. FDA Benefit/Risk Assessment

Surgical mesh placed in the anterior vaginal compartment to treat POP is a permanent implant in the case of polypropylene mesh and a semi-permanent implant in the case of biologic mesh. To assess the benefit/risk of an individual device of this type, the FDA believes a comparison should be made to native tissue repair either through a randomized control trial or parallel cohort study. The FDA believes this comparison is important to establish favorable benefit/risk, because the use of surgical mesh should offer an advantage over the same repair without use of mesh. This advantage may be specific to a certain patient population or over the lifetime of the repair.

As evidenced by the literature review, the risk profile for mesh is less favorable compared to native tissue repair. Mesh erosion/exposure is a risk specific to patients who undergo a mesh repair and occurs at a rate of approximately 11-18%. Mesh erosion/exposure may require surgical revision and/or removal, which puts patients with these devices at greater risk for reoperation for all indications (recurrence and erosions/exposure). In addition, some types of adverse events for mesh are likely to increase over time as compared to native tissue repair, given the mesh is intended to remain in place for the rest of the patient's life. Evidence from RCTs demonstrate that at 12, 24, and 36 months, safety outcomes favor native tissue repair. In addition, new-onset mesh-specific adverse events (erosions/exposures) can occur as late as the third year postoperation. To comprehensively evaluate safety between mesh and native tissue repair, the FDA believes that all adverse events (not just those designated as device or procedure related adverse events) should be considered, along with their severity/seriousness, timing, resolution, and relatedness to the device and/or procedure.

Accordingly, given its increased risks, to establish a favorable benefit/risk, the FDA believes that mesh placed in the anterior vaginal compartment to treat POP should be more effective (*i.e.*, statistically superior) than native tissue repair. When assessing effectiveness, the FDA believes both anatomic and subjective outcomes should be considered, as well as the need for retreatment for prolapse. The FDA acknowledges that subjective outcomes can be challenging to evaluate because patients may have different perceptions of the same symptoms (*i.e.*, patients may find different symptoms bothersome and their perception of those symptoms may change over time). When assessing safety, the FDA believes the adverse event profile for mesh placed in the anterior vaginal compartment should be comparable to native tissue repair, or any increase in risk be offset by a corresponding improvement in effectiveness. The FDA understands that patients and physicians may be willing to take on greater safety risk with increased likelihood or magnitude of effectiveness (*e.g.*, patients with recurrent prolapse). Because this device type is an implant, the FDA believes that favorable/benefit risk should be established long term. To support a marketing application, the FDA believes that safety and effectiveness outcomes beyond 12-months are necessary, with continued postmarket follow up to

evaluate long term adverse events and durability of the repair. There are limited long term data in the literature, particularly beyond three years; however, the available data support the potential for decreased effectiveness and new onset adverse events over time. Furthermore, surgical mesh is an implant that is intended to provide long term repair of POP.

However, there are several study design considerations that introduce uncertainty into a benefit/risk determination. The FDA believes the following considerations are important to clinical studies specifically evaluating mesh:

- Different patient characteristics between mesh and native tissue arms (potentially including severity of prolapse, age, sexual activity, BMI (may be an indicator of co-morbidity), menopausal status, medical and surgical history (hysterectomy, previous prolapse repair), and concomitant procedures (particularly sling placement to prophylactically treat occult SUI)
- Different surgeon experience between the mesh and native tissue repair arms and how representative surgeon experience is of future users in a real-world setting
- Lack of blinding for assessment of anatomic outcome

Our literature review found that patient factors such as age and obesity may affect safety and/or effectiveness outcomes with mesh. In addition, patient factors such as parity, premenopausal estrogen therapy, diabetes, and smoking may be risk factors for erosion. Concomitant procedures such as sling placement and hysterectomy may also affect safety and effectiveness outcomes when using mesh. However, there is conflicting evidence in the literature regarding many of these patient factors. Finally, the literature also supports that high volume/more experienced physicians have improved safety and effectiveness outcomes with mesh.

The following considerations while not specific to mesh studies are also important to consider when evaluating safety and effectiveness outcomes:

- Differences in how patients are assigned to device versus control groups (*e.g.*, mesh versus native tissue repair)
- Potential for site selection bias (more complex cases being sent to specialty centers to get better outcomes)
- Lack of collection of all adverse events and inconsistent adjudication of adverse events (related versus unrelated)
- Potential for real world use to be worse than study outcomes
- Significant loss to follow up, particularly if follow up rates are different between arms (which may be caused by adverse events)

The FDA is requesting Panel input and recommendations on how to evaluate benefit/risk for mesh placed in the anterior vaginal compartment to treat POP in light of these potential study design considerations.

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Appendix 1 – Literature Review Methods and Strengths and Limitations

The PubMed database was searched using the following search strategy:

> ("pelvic organ prolapse" [MeSH terms]) AND ("surgical mesh" OR "transvaginal mesh" OR "vaginal mesh")

The final search was conducted on November 1, 2018; therefore, the date range of the search was January 1, 2008 through November 1, 2018.

The eligibility criteria for inclusion in the literature review were as follows:

1. English
2. Relevant to transvaginal mesh (any brand/type) used for anterior and/or apical pelvic organ prolapse repair; mesh repair for posterior prolapse is not excluded but must include anterior/apical as well
3. Clinical research study with live human participants OR meta-analysis of randomized controlled trials
4. Article presents clinical outcome data (safety and/or effectiveness) for at least 12 months of patient follow-up, and at least 25 patients
5. For cohort studies: article presents prospectively collected data relevant to at least one device of interest

The search resulted in 1,339 results in PubMed. After review of the abstracts and full text articles, 1,267 articles were excluded for the following reasons:

1. Non-English: n=133
2. Non-clinical study:
    a. Review article without meta-analysis or new data presented: n=179
    b. Editorial/comment without new data presented: n=157
    c. Video demonstration: n=18
    d. Bench study: n=17
    e. Animal study: n=16
    f. Cadaver study: n=11
    g. Description of study or registry protocol, no clinical data: n=5
    h. Bibliography: n=2
3. Clinical study:
    a. Retrospective data collection or chart review: n=217
    b. Relevance (*e.g.*, studies related to rectopexy, surgical method, etc.): n=166
    c. Prospective cohort study which did not study a currently marketed device (Uphold or Uphold LITE, Restorelle or Restorelle DirectFix Anterior, or Xenform): n=152
    d. Case series or report: n=121
    e. Pilot study: n=31
    f. Study with no clinical outcome data (*e.g.*, trends in clinical practice, cost analysis): n=17
    g. Case-control or cross-sectional study: n=12
    h. Study with less than one year follow-up: n=7
    i. Study including posterior repair only, no anterior or apical repair: n=6

After exclusions, 72 articles remained for review, with the following study designs:

1. Randomized controlled trials (RCT): n=39
2. Prospective cohort with a currently marketed device (Uphold or Uphold LITE, Restorelle or Restorelle DirectFix Anterior, or Xenform): n=7
3. Large database or registry study: n=14
4. Meta-analysis of RCTs: n=9
5. Markov analysis: n=3

The selected articles are summarized in the data extraction tables at the end of the review, as follows:

Table 1: Meta-analyses, study design
Table 2: Meta-analyses, effectiveness results
Table 3: Meta-analyses, safety results
Table 4: Database studies, study design
Table 5: Database studies, results
Table 6: RCTs, study design (note: only includes RCTs that randomized subjects to mesh versus non-mesh surgery; other RCTs are presented in text only)
Table 7: RCTs with one year follow-up, results
Table 8: RCTs with two years follow-up, results
Table 9: RCTs with three years follow-up, results
Table 10: Prospective cohort studies for Uphold LITE, Xenform, or Restorelle DirectFix Anterior meshes

Multiple mesh materials were represented in the literature, including non-absorbable synthetic mesh (usually made of polypropylene), biologic graft, and, absorbable synthetic (such as polyglactin). Large database studies usually were not able to identify brand of mesh, and meta-analyses generally considered all types together or stratified by material (*e.g.*, synthetic versus biologic). However, some RCTs and prospective cohort studies identified the brand of mesh used. Only prospective cohort studies with currently marketed device (Uphold or Uphold Lite, Restorelle or Restorelle DirectFix Anterior, or Xenform) were included in the review; others were excluded.

Studies varied on inclusion criteria and what types of repairs were performed. Some restricted participants by age (*e.g.*, over 65). Some studies focused only on one type of repair (*e.g.* anterior repair) while others allowed concomitant repair of the posterior compartment, SUI sling surgery, and/or hysterectomy. Most studies used native tissue repair as a comparison or control group, although there were some that used other procedures such as abdominal or laparoscopic sacrocolpopexy as a comparison. Most included between one to three years of follow-up, although there were a couple studies with longer follow-up, up to six years.

The strengths of this review include the relatively large number of articles with a high level of evidence, including RCTs and meta-analyses of RCTs. In addition, several studies included analysis of a large database of real world evidence, to shed light on outcomes experienced by real world patients. Most authors attempted to minimize bias and confounding by blinding of investigators and patients when possible, multivariate adjustment, and in some cases, propensity score matching. It should be noted that some published RCT results reflected a secondary analysis of the data rather than the primary aim of the study, [16, 36-38] and therefore there may be a risk of false positive results due to multiple comparisons that were not statistically powered.

The largest limitation of this review is the heterogeneity of articles included, regarding prolapse compartment (anterior, apical, posterior), length of follow-up, inclusion/exclusion criteria (especially

patient age), and comparison groups. Definition of certain outcomes may also differ by article, especially repeat surgery or reintervention. This may sometimes include surgeries to revise or remove mesh due to complications, and sometimes only include repeat prolapse repairs. The data extraction tables note the definition of this variable when specified by the article. In this review, repeat surgery is considered an effectiveness outcome, although it may be due to a complication or safety event. Even anatomic outcomes based on the POP-Q varied by whether success was considered to be prolapse stage less than 1 or less than 2. Therefore, it is difficult to make larger conclusions for the benefit and risk of vaginal mesh, or comparisons between different types of mesh or types of surgical procedures.

Randomized controlled trials generally attempted to minimize bias by blinding investigators and patients when possible; for example, having a blinded physician who did not perform the surgery measure the study outcome (such as POP-Q exam). However, sometimes the physician may become unblinded during a follow-up visit due to mesh that is visible or palpable upon exam. This may be unavoidable, although it is unclear if it would affect the results of the POP-Q exam since it should be based on objective measurements of prolapse and vaginal length. In some instances, studies did not attempt to blind/mask the physician or patient (such as cohort studies which did not randomize patients to treatment arm).

Often it is helpful to know if study authors have a financial relationship with the company, including funding provided for the study, because it may be associated with positive publication bias. The Cochrane reviews are funded by the Cochrane Collaboration and data extraction is systematically performed by multiple reviewers, usually researchers in the field, and articles are rated for risk of bias; therefore, conclusions are considered fairly objective. However, their conclusions are limited to the RCT studies available to review, which are sometimes funded by industry. Four of the RCTs reviewed included an industry funding source, although some authors noted that the industry partner did not have influence over the data or published results. Notably, the largest RCT, the PROSPECT trial, was funded with an NIH grant rather than industry funding. Some other studies, such as database studies, did not disclose any financial relationship with industry.

It should be noted that sometimes multiple articles were published by the same group of authors, sometimes with overlapping datasets. When obvious, this was noted in the footnotes of the tables, and results were combined across publications.

This review includes some articles published by authors outside of the U.S., mostly from Scandinavia, Western Europe, China, Japan, and Australia. Practice differences between the U.S. and other countries are outside the scope of this review, but it is noted that there may be important differences in factors such as availability of mesh brands, practice guidelines for surgeons, and health insurance coverage.

The above limitations should be considered while interpreting the results presented.

Appendix II – Literature Review Tables

Meta-analyses

Table A1. Meta-analyses: Study Design							
Author, Year	**Publication Years**	**Number of RCTs with mesh group**	**Total Number of Mesh Patients (when specified), Type of Repair**	**Comparison Group (n, type)**	**Length of Follow-up**	**Effectiveness Endpoints**	**Safety Endpoints**
Coolen, 2017[67]	Through 4/25/17	2	176, Post-hysterectomy apical repair (Prolift)	165, Sacrospinal Fixation	12 months	Reoperation	Complications
Maher, 2017[27]*	Through 8/23/16	16	986, Polypropylene mesh 274, Biological graft Anterior	990, Native tissue repair	1-5 years	Repeat surgery Awareness of Prolapse Recurrence POP-Q Quality of life	De novo SUI Mesh exposure Bladder injury
Sun, 2016[58]	1990-2015	11	684, Anterior	670, Colporrhaphy	6-36 months	POP-Q Satisfaction Sexual Activity	Urinary retention Urinary incontinence Voiding difficulty Dyspareunia Vaginal bulge Urinary tract infection Mesh exposure
Deng, 2016[56]	Through December 2014	25 (included cohort studies and SUI patients)	5270, Anterior, Posterior	None	4-52 months	None	Mesh erosion

Table A1. Meta-analyses: Study Design							
Author, Year	**Publication Years**	**Number of RCTs with mesh group**	**Total Number of Mesh Patients (when specified), Type of Repair**	**Comparison Group (n, type)**	**Length of Follow-up**	**Effectiveness Endpoints**	**Safety Endpoints**
Juliato, 2016[68]	2000-2015	12	Anterior (synthetic absorbable mesh)	Colporrhaphy	1-3 years	Objective Cure Reoperation Quality of Life	Complications
Maher, 2016a[28] *	Through 7/6/15	37	Anterior, apical, posterior	NTR	1-3 years	Repeat surgery Awareness of Prolapse Recurrence Quality of Life	Bladder injury De novo dyspareunia De novo SUI
Maher, 2016b[49] *	Through 7/6/15	24	Apical	No mesh	2-4 years	Repeat surgery Awareness of Prolapse Recurrence Quality of Life	Bladder injury De novo dyspareunia De novo SUI
Min, 2013[69]	1980-February 2012	20	1,100, Anterior	1,100	3-24 months	Failure Recurrence	Mesh exposure De novo SUI De novo dyspareunia Pelvic pain
Jia, 2008[70]	1980-2008	17	640, Anterior/Posterior	1862, no mesh	≥1 year	Prolapse Symptoms Recurrence Resurgery Persistent urinary symptoms, bowel symptoms, and dyspareunia	Mesh erosion

*Cochrane Review

Table A2. Meta-analyses: Main Results, Effectiveness Endpoints				
Author, Year	**Mesh**	**Non-mesh**	**Between-group comparisons (Mesh vs. non-mesh unless otherwise noted)**	**Favors (based on statistical significance)**
Coolen, 2017	Reoperation for POP: 6/117 (5.1%)	SSF: Reoperations: 1/121 (0.08%)	OR: 4.46 (0.72-27.43)	Neither
Maher, 2017 (Anterior)	<u>Biological Graft</u> Awareness of prolapse: 34/274 (12.4%) Repeat POP surgery: 14/319 (4.4%) Recurrence: 89/346 (25.7%)	Awareness of prolapse: 34/278 (12.2%) Repeat POP surgery: 17/331 (5.1%) Recurrence: 119/355 (33.5%)	<u>Biological Graft (non-mesh vs. mesh)</u> Awareness of prolapse: RR=0.98 (0.52-1.82) Repeat POP surgery: RR=1.02 (0.53-1.97) Repeat surgery for POP, SUI, or exposure: N/A Recurrence: RR=1.32 (1.06-1.65)* QoL: no differences	 Neither Neither N/A Mesh Neither
	<u>Polypropylene</u> Awareness of prolapse: 74/569 (13.0%) Repeat POP surgery: 15/818 (1.8%) Repeat surgery for POP, SUI, or exposure: 75/771 (9.7%) Recurrence: 124/986 (12.6%)	Awareness of prolapse: 129/564 (22.9%) Repeat POP surgery: 32/811 (3.9%) Repeat surgery for POP, SUI, or exposure: 41/756 (5.4%) Recurrence: 374/990 (37.8%)	<u>Polypropylene (non-mesh vs. mesh)</u> Awareness of prolapse: RR=1.77 (1.37-2.28)* Repeat POP surgery: RR=2.03 (1.15-3.58)* Repeat surgery for POP, SUI, or exposure: RR=0.59 (0.41-0.83) Recurrence: RR=3.01 (2.52-3.60)* QoL: no differences	 Mesh Mesh NTR Mesh Neither
Sun, 2016	POP-Q<II: 81.3% (39.5-95.2%) Satisfaction: 60.4% (20.0-97.3%) Sexual function: 49.3% (31.0-90.0%)	POP-Q<II: 56.6% (28.3-90.9%) Satisfaction: 52.7% (40.1-92.6%) Sexual function: 48.6% (9.5-85.0%)	POP-Q<II: RR=1.44 (1.34-1.55)* Satisfaction: RR=1.10 (0.96-1.26) Sexual function: RR=1.03 (0.90-1.11)	Mesh Neither Neither
Juliato, 2016	Recurrence: 19/300 (6.3%) Objective cure: 551/781 (70.6%) Subjective cure: 135/144 (93.6%) Reoperation: 15/183 (8.2%)	Recurrence: 62/285 (21.8%) Objective cure: 418/759 (55.1%) Subjective cure: 122/138 (88.4%) Reoperation: 21/174 (12.1%)	Recurrence: OR=0.22 (0.13-0.38)* Objective cure: OR=1.28 (1.07-1.53)* Subjective cure: OR=0.65 (0.83-1.29) Reoperation: OR=0.65 (0.83-4.51) Quality of Life (PISQ-12, P-QOL, PFIQ-7, PFDI-20): ns	Mesh Mesh Neither Neither Neither

Table A2. Meta-analyses: Main Results, Effectiveness Endpoints				
Author, Year	**Mesh**	**Non-mesh**	**Between-group comparisons (Mesh vs. non-mesh unless otherwise noted)**	**Favors (based on statistical significance)**
Maher, 2016a (Anterior, Apical, Posterior)	Awareness of prolapse: 119/812 (14.7%) Repeat POP surgery: 19/841 (2.3%) Repeat surgery for POP, SUI, or exposure: 57/439 (13.0%) Recurrence: 221/1251 (17.7%)	Awareness of prolapse: 177/802 (22.1%) Repeat POP surgery: 38/834 (4.6%) Repeat surgery for POP, SUI, or exposure: 23/428 (5.4%) Recurrence: 526/1243 (42.3%)	Awareness of prolapse: RR=0.66 (0.54-0.81) Repeat POP surgery: RR=0.53 (0.31-0.88) Repeat surgery for POP, SUI, or exposure: RR=2.40 (1.51-3.81) Recurrence: RR=0.40 (0.30-0.53)	Mesh Mesh NTR Mesh
Maher, 2016b (Apical)	Awareness of prolapse: 5/26 Repeat POP surgery: 8/259 Recurrence: 30/140	Awareness of prolapse: 5/28 (17.9%) Repeat POP surgery: 11/238 (4.6%) Recurrence: 65/129 (50.4%)	Awareness of prolapse: RR=1.08 (0.35-3.30) Repeat POP surgery: RR=0.69 (0.30-1.60) Recurrence: RR=0.36 (0.09-1.40)	Neither Neither Neither
Min, 2013	Failure rate: 207/1100 (18.8%)	Failure rate: 422/1100 (38.4%)	Failure rate: RR=0.51 (0.41-0.64)*	Mesh
Jia, 2008	Recurrence: 77/557 (13.8%)	Recurrence: 179/591 (30.3%)	Overall Recurrence: RR=0.48 (0.32-0.72)*	 Mesh
	Recurrence: 52/161 (32.3%)	Recurrence: 184/640 (28.8%)	Absorbable Synthetic Recurrence: aOR=0.82 (0.50-1.32)	 Neither
	Recurrence: 120/555 (21.6%)	Recurrence: 184/640 (28.8%)	Biological Graft Recurrence: aOR=0.51 (0.36-0.72)*	 Mesh
	Recurrence: 41/344 (11.9%)	Recurrence: 184/640 (28.8%)	Nonabsorbable Synthetic Recurrence: aOR=0.19 (0.12-0.30)*	 Mesh

*Statistically significant difference (ranges in parentheses represent 95% confidence intervals)

Abbreviations: aOR=adjusted odds ratio, RR=risk ratio, ns=not significant, N/A=not applicable or available; SSF=Sacrospinal Fixation

Note: some meta-analyses presented number of events over number of patients combined over several studies and did not provide percentages; data is presented in the way the authors presented originally.

Table A3. Meta-analyses: Main Results, Safety Endpoints				
Author, Year	**Mesh**	**Non-mesh**	**Between-Group Comparisons**	**Favors (based on statistical significance)**
Coolen, 2017	Complications: 3/117 (2.6%)	Complications: 1/121 (0.8%)	OR=0.33 (0.03-3.27) (ns)	Neither
Maher, 2017 (anterior)	<u>Biological Graft</u> SUI: 14/108 (13.0%) Dyspareunia: 11/74 (14.9%) Voiding dysfunction: 21/74 (28.4%)	SUI: 19/110 (17.3%) Dyspareunia: 10/77 (13.0%) Voiding dysfunction: 24/81 (30.0%)	<u>Biological Graft (non-mesh vs. mesh)</u> De novo SUI: RR=1.44 (0.79-2.64) (ns) Dyspareunia: RR=0.87 (0.39-1.93) (ns) Voiding dysfunction: RR=1.13 (0.71-1.80)	 Neither Neither Neither
	<u>Polypropylene</u> SUI: 49/479 (10.2%) Dyspareunia: 21/293 (7.2%) Voiding dysfunction: 3/137 (2.2%) Mesh erosion: 101/896 (11.3%)	SUI: 32/478 (6.7%) Dyspareunia: 11/290 (3.8%) Voiding dysfunction: 4/140 (2.9%)	<u>Polypropylene (non-mesh vs. mesh)</u> De novo SUI: RR=0.67 (0.44-1.01) (ns) Dyspareunia: RR=0.54 (0.27-1.06) Voiding dysfunction: RR=1.22 (0.33-4.47)	 Neither Neither Neither
Sun, 2016	Urinary retention: 5.2% Urinary incontinence: 10.3% Voiding difficulty: 6.9% Dyspareunia: 12.2% Vaginal bulge: 43.5% Urinary tract infection: 8.8% Mesh exposure: 5.4%	Urinary retention: 4.4% Urinary incontinence: 10.7% Voiding difficulty: 6.3% Dyspareunia: 10.0% Vaginal bulge: 39.4% Urinary tract infection: 7.5%	Urinary retention: RR=1.12 (0.65-1.94) Urinary incontinence: RR=1.01 (0.63-1.63) Voiding difficulty: RR=1.11 (0.69-1.80) Dyspareunia: RR=1.21 (0.87-1.67) Vaginal bulge: RR=1.08 (0.93-1.25) Urinary tract infection: RR=1.15 (0.74-1.78)	Neither Neither Neither Neither Neither Neither
Deng, 2016	Mesh erosion: 7.4%	N/A	N/A	NTR
Juliato, 2016	Dyspareunia: 15/193 (7.8%) Mesh erosion: 7.4% (3.2-19%)	Dyspareunia: 16/204 (7.8%)	Dyspareunia: OR=0.94 (0.45-1.96)	Neither
Maher, 2016a (Anterior, Apical, Posterior)	Mesh exposure: 12% Bladder injury: 22/772 (2.8%) SUI: 106/755 (14.0%) Dyspareunia: 30/389 (7.7%)	Bladder injury: 4/742 (0.5%) SUI: 73/757 (9.6%) Dyspareunia: 31/375 (8.3%)	Bladder injury: RR=3.92 (1.62-9.50) SUI: RR=1.39 (1.06-1.82) Dyspareunia: RR=0.92 (0.58-1.47)	NTR NTR Neither

Table A3. Meta-analyses: Main Results, Safety Endpoints				
Author, Year	**Mesh**	**Non-mesh**	**Between-Group Comparisons**	**Favors (based on statistical significance)**
Maher, 2016b (Apical)	Mesh exposure: 18% Surgery for mesh exposure: 9.5% SUI: 47/149 (31.5%) Dyspareunia: 13/258 (5.0%) Bladder injury: 10/226 (4.4%)	Mesh exposure: N/A SUI: 32/146 (22.0%) Dyspareunia: 10/243 (4.1%) Bladder injury: 3/219 (1.4%)	Mesh exposure: N/A SUI: RR=1.37 (0.94-1.99) Dyspareunia: RR=1.21 (0.55-2.66) Bladder injury: RR=3.00 (0.91-9.89)	NTR Neither Neither Neither
Min, 2013	Overall Postoperative pain: 24/300 (8.0%) UTI: 19/214 (8.8%) De novo SUI: 26/323 (8.0%) De novo dyspareunia: 11/175 (6.3%)	Postoperative pain: 17/302 (5.6%) UTI: 33/205 (16.1%) De novo SUI: 34/318 (10.7%) De novo dyspareunia: 13/174 (7.5%)	Postoperative pain: RR=1.40 (0.38-5.13) UTI: RR=0.56 (0.31-1.02) De novo SUI: RR=0.72 (0.25-2.06) De novo dyspareunia: 0.81 (0.37-1.76)	Neither Neither Neither Neither
	Synthetic mesh Mesh exposure: 5.32% (3.23-17.31%) Mesh erosion: 10.61% (6.52-14.81%)	N/A	N/A	
	Biological graft Mesh exposure: 0.78% (0.00-1.00%) Mesh erosion: 2.53% (0.00-4.17%)	N/A	N/A	
Jia, 2008	Nonabsorbable synthetic Mesh erosion: 68/666 (10.2%)	N/A	N/A	
	Absorbable synthetic Mesh erosion: 1/147 (0.7%)	N/A	N/A	
	Biological graft Mesh erosion: 35/581 (6.0%)	N/A	N/A	

Database Studies

Table A4. Database Studies: Study Design								
Author, Year	**Data Source**	**Years**	**Length of f/u (yrs)**	**N (mesh)**	**N (non-mesh POP repair)**	**Comparisons**	**Effectiveness Outcomes**	**Safety Outcomes**
Dandolu, 2017[32]	Truven CCAE, Medicare Supplemental databases	2008-2013	2	20,760	11,570	Mesh vs. sacrocolpopexy Mesh vs. NTR	Failure (use of pessary, reoperation for POP)	Mesh removal/revision
Forde, 2017[36]	New York Statewide Planning and Research Cooperative System (SPARCS)	2009-2014	3	1,601	N/A	Mesh repair with vs. without concomitant hysterectomy	Reintervention (repeat prolapse and mesh revision procedures)	Urinary retention Pain
Chughtai, 2017a[64]	SPARCS	2008-2012	1	8,868 (5,070 with sling, 3,798 without sling)	N/A	Mesh with vs. without concomitant sling procedure	Reintervention (repeat POP surgery or mesh revision/removal)	Mesh complications
Chughtai, 2017b[62]	SPARCS	2008-2009	6	2,102	7,338 Vaginal Hysterectomy	Mesh-based POP surgery vs. vaginal hysterectomy	N/A	Autoimmune Disease
Eilber, 2017[66]	Medicare Public Use Files	2007-2008	1	1,657	0	Surgeon volume (low, medium, high)	Reoperation (repeat POP surgery or mesh revision/removal)	N/A
Morling, 2017[33]	Scotland National Hospital Admission Database	1997-1998, 2015-2016	5	278	3,866	Mesh vs. no mesh	Repeat POP surgery	Complications

Table A4. Database Studies: Study Design								
Author, Year	**Data Source**	**Years**	**Length of f/u (yrs)**	**N (mesh)**	**N (non-mesh POP repair)**	**Comparisons**	**Effectiveness Outcomes**	**Safety Outcomes**
Bohlin, 2017[71]	Swedish National Register for Gynaecological Surgery	2006-2015	1	1,214	1,507	Mesh vs. no mesh	Cure Bulge	Complications
Chughtai, 2015[34]	SPARCS	2008-2011	1	7,338	20,653	Mesh vs. no mesh	Reinterventions (repeat POP surgery or mesh revision)	Complications (90 days post op)
Nussler, 2015[31]	Swedish National Register for Gynaecological Surgery	2006-2013	1	356	6,247	Mesh vs. no mesh	Cure Reoperation (reason not specified) Satisfaction Improvement	Complications (patient reported) Complications (surgeon reported) Bladder Injury
Anger, 2014[35]	Medicare	1999-2008	1	1,804	16,909	Mesh vs. no mesh (may have concomitant sling)	Reoperation for POP Removal	Complications Urinary Retention Pelvic pain including dyspareunia
Bjelic-Radisic, 2014[72]	Austrian Transvaginal Mesh Registry	2006-2010	1	726	0	N/A	None	Complications Mesh exposure Do novo bladder symptoms Dyspareunia
Jonsson, 2013[30]	Marketscan	2005-2010	5	6,871	20,938	Mesh vs. NTR	Repeat POP surgery	Surgery for mesh complications

Table A4. Database Studies: Study Design								
Author, Year	**Data Source**	**Years**	**Length of f/u (yrs)**	**N (mesh)**	**N (non-mesh POP repair)**	**Comparisons**	**Effectiveness Outcomes**	**Safety Outcomes**
Nussler, 2013[29]	Swedish National Register for Gynaecological Surgery	2008-2010	1	129	157	Mesh vs. no mesh	Patient reported cure (feeling of protrusion) Reoperation	Patient reported complications Physician reported complications Infection
Nguyen, 2012[73]	Kaiser Permanente Southern and Northern California and Hawaii	2008-2010	1	4,142	N/A	Anterior vs. posterior vs. apical	N/A	Mesh revision/removal

Table A5. Database Studies: Main Results				
Author, Year	**Effectiveness (Mesh vs. NTR)**	**Favors**	**Safety (Mesh vs. NTR)**	**Favors (based on statistical significance)**
Dandolu, 2017	Reoperation for POP: 5.0% vs. 3.8% Reoperation or pessary: 6.2% vs. 5.2%	NTR NTR	Mesh removal/revision: 5.1% Dyspareunia: 6.1% vs. 7.5% Pelvic pain: 16.4% vs. 22.0%	Mesh N/A N/A
Forde, 2017	Reintervention at 1 yr: 3.1% vs. 4.6% (ns) Reintervention at 3 yr: 6.6% vs. 6.6% (ns)	Neither	Complications: 2.5% vs. 1.7%* Urinary retention: 7.7% vs. 9.7% (ns) Pelvic pain: ns	NTR NTR Neither
Chughtai, 2017a	Without sling Resurgery: 4.3%	N/A	Without sling Erosions: 1.9%	N/A
	With sling Resurgery: 5.6%	N/A	With sling Erosions: 2.7%	N/A
Chughtai, 2017b	N/A	N/A	Autoimmune disease: aOR=0.78 (0.48-1.26) Compared to vaginal hysterectomy	N/A
Eilber, 2017	Reoperation rate: Low volume surgeons 6% Intermediate volume surgeons 2% High volume surgeons 3%	N/A	N/A	N/A
Morling, 2017	Repeat POP surgery: RR=1.69 (1.29-2.20)*	NTR	Complications: RR=0.93 (0.49-1.79) (ns)	Neither
Bohlin, 2017	Cure: 86.4% vs. 77.3%* Satisfaction: 81.0% vs. 68.2%* Improvement: 91.7% vs. 78.2%*	Mesh Mesh Mesh	De novo UI: 13.1% vs. 14.9% (ns)	Neither
Chughtai, 2015	Reintervention: HR=1.47 (1.21-1.79)*	NTR	Urinary retention at 90 days post op: RR=1.33 (1.18-1.51)*	NTR
Nussler, 2015	Cure: OR=1.53 (1.1-2.13)* Reoperation: OR=6.87 (3.68-12.80)* Satisfaction: OR=2.45 (1.62-5.54)* Improvement: OR=2.99 (1.62-5.54)*	Mesh NTR Mesh Mesh	Complications (patient-reported): OR=1.51 (1.15-1.98) Complications (surgeon-reported): OR=2.27 (1.77-2.91) Bladder injury: OR=6.71 (3.14-14.33)	NTR NTR NTR

Table A5. Database Studies: Main Results				
Author, Year	**Effectiveness (Mesh vs. NTR)**	**Favors**	**Safety (Mesh vs. NTR)**	**Favors (based on statistical significance)**
Anger, 2014	Reoperation for POP: 4% vs. 6%*	Mesh	Mesh removal: 4% vs. 1%* UTI: 41% vs. 38%* Pelvic pain: 27% vs. 19%* Urinary retention: 17% vs. 13%*	NTR NTR NTR NTR
Bjelic-Radisic, 2014	Satisfaction (patient): 86% Satisfaction (physician): 81%	N/A	Complications 6.8% Mesh exposure 12% Do novo bladder symptoms 11% Dyspareunia 10%	N/A
Jonsson, 2013	Surgery for recurrent prolapse: 10.4% vs. 9.3%	NTR	Surgery for mesh complications: 5.9% vs. 0.7%	NTR
Nussler, 2013	Feeling of protrusion: aOR=2.90 (1.34-6.31)* Satisfaction: aOR=3.0 (1.52-5.92)*	Mesh Mesh	Patient reported complications: aOR=2.26 (1.12-4.56)* Physician reported complications: aOR=3.06 (1.64-5.73)* Infection: aOR=3.90 (1.07-14.25)* Urinary retention: aOR=1.38 (0.30-6.38)	NTR NTR NTR NTR
Nguyen, 2012	N/A	N/A	Anterior Resurgery for mesh exposure: 6%*	N/A
	N/A	N/A	Posterior Resurgery for mesh exposure: 2%	N/A
	N/A	N/A	Apical Resurgery for mesh exposure: 2%	N/A

*Statistically significant between group difference
Abbreviations: ns=not statistically significant, HR=hazard ratio, OR=odds ratio, aOR=adjusted odds ratio, RR=risk ratio

Randomized Controlled Trials

Table A6. Randomized Controlled Trials: Study Design										
Author, Year	Country	Device Evaluated	Manufacturer	Material	Mesh n	Control n	Length of follow-up (yrs)	Compartment Repair		
								Anterior	Apical	Posterior
Robert, 2014[55]	Canada	Not specified	Not specified[a]	Biologic (porcine)	28	29	1	Yes	Yes	No
Rudnicki, 2014[53]	Norway, Sweden, Finland, Denmark	Avaulta Plus	Bard	Biosynthetic (polypropylene coated with film of porcine collagen)	79	82	1	Yes	No	Yes
Vollebregt, 2011[59]	Netherlands	Avaulta	Bard	Polypropylene	61	64	1	Yes	Yes	Yes
Carey, 2009[74]	Australia	Gynemesh	Ethicon	Polypropylene	69	70	1	Yes	Yes	Yes
Lopes, 2010[75]	Brazil	Nazca R	Promedon	Polypropylene	16	16	1	Yes	Yes	Yes
Delroy, 2013[76]	Brazil	Nazca TC[b]	Promedon	Polypropylene	40	39	1	Yes	Yes	Yes
Sivaslioglu, 2008[77]	Turkey	Parietene	Sofradim	Polypropylene	45	45	1	Yes	No	No
Nguyen, 2008[78]	US	Perigee, IntePro	AMS	Polypropylene	37	38	1	Yes	No	No
Altman, 2011[65]	Sweden, Norway, Finland, Denmark	Prolift	Ethicon	Polypropylene	200	189	1	Yes	No	No
Milani, 2011[79]	Netherlands	Prolift	Ethicon	Polypropylene	32	28	1	Yes	Yes	Yes
Ek, 2013[80]	Sweden	Prolift	Ethicon	Polypropylene	60	39	1	Yes	No	No
Halaska, 2012[81]	Czech Republic	Prolift	Ethicon	Polypropylene	85	83	1	Yes	Yes	Yes

Table A6. Randomized Controlled Trials: Study Design										
Author, Year	Country	Device Evaluated	Manufacturer	Material	Mesh n	Control n	Length of follow-up (yrs)	Compartment Repair		
								Anterior	Apical	Posterior
dos Reis Brandao da Silveira, 2015[82]	Brazil	Prolift	Ethicon	Polypropylene	94	90	1	Yes	Yes	Yes
Withagen, 2012[83]; Withagen, 2011[84]	Netherlands	Prolift	Ethicon	Polypropylene	95	99	1	Yes	Yes	Yes
Svabik, 2014[85]	Czech Republic	Prolift Total	Ethicon	Polypropylene	36[c]	34[c]	1	Yes	Yes	Yes
de Tayrac, 2013[86]	France	Ugytex	Sofradim-Covidien	Polypropylene	75	72	1	Yes	No	No
Glazener, 2016[38]; Glazener, 2017[37]	UK	Not specified	Not specified	Biologic (porcine or bovine), Synthetic	803	545	2	Yes	Yes	Yes
Menefee, 2011[87]	US	Pelvicol, Not specified	Bard, Not specified[a]	Biologic (porcine), Polypropylene	66	33	2	Yes	Yes	Yes
Minassian, 2014[88]	US	Vicryl	Ethicon	Polyglactin	35	35[d]	2	Yes	Yes	Yes
Madhuvrata, 2011[89]	Scotland	Vicryl	Ethicon	Polyglactin	32	34	2	Yes	No	Yes
El-Nazer, 2012[90]	Egypt	Gynemesh	Ethicon	Polypropylene	21	23	2	Yes	No	No
Dias, 2016[91]	Brazil	Nazca TC[b]	Promedon	Polypropylene	43	43	2	Yes	No	Yes

Table A6. Randomized Controlled Trials: Study Design										
Author, Year	Country	Device Evaluated	Manufacturer	Material	Mesh n	Control n	Length of follow-up (yrs)	Compartment Repair		
								Anterior	Apical	Posterior
Tamanini, 2015 [92]; Tamanini, 2013a[93]; Tamanini, 2013b[94]	Brazil	Nazca TC[b]	Promedon	Polypropylene	45	55	2	Yes	Yes	Yes
Lamblin, 2014[95]	France	Perigee	AMS	Polypropylene	33	35	2	Yes	Yes	No
Maher, 2011[96][e]	Australia	Prolift	Ethicon	Polypropylene	55	53	2	Yes	Yes	Yes
Damiani, 2016[97]	Italy	Avaulta Solo, Pelvisoft	Bard, Bard	Polypropylene, Biologic (porcine)	58	59	2	Yes	Yes	Yes
Dahlgren, 2011[98]	Sweden	Pelvicol	Bard	Biologic (porcine)	68	64	3	Yes	Yes	Yes
Rudnicki, 2016[54]	Norway, Sweden, Finland, Denmark	Avaulta Plus	Bard	Biosynthetic (polypropylene coated with film of porcine collagen)	70	68	3	Yes	No	No
Nieminen, 2010[57]	Finland	Parietene Light	Sofradim	Polypropylene	105	97	3	Yes	No	Yes
Gutman, 2013[51]; Shveiky, 2012[51]; Sokol, 2012[52]	US	Prolift	Ethicon	Polypropylene	33	32	3	Yes	Yes	Yes

[a]Article did not specify the brand of mesh used; however, study was funded by a manufacturer.
[b]Three articles presented data from the same surgical center, with different but overlapping years of data collection; thus, these articles are likely to have overlapping groups of subjects.
[c]All subjects had post-hysterectomy prolapse and unilateral or bilateral levator ani avulsion injury.
[d]Control group received abdominal paravaginal defect repair.
[e]Control group received laparoscopic sacrocolpopexy.

Table A7. Randomized Controlled Trials with One Year Follow-up: Main Results				
Author, Year	**Effectiveness Results Mesh vs. NTR (statistical significance)**	**Favors**	**Safety Results Mesh vs. NTR (statistical significance)**	**Favors (based on statistical significance)**
Robert, 2014	POP-Q Ba≤-1: 56% vs. 61% (ns) POP-Q ≤2: 82% vs. 59%* Recurrence: 7% vs. 7% (ns) PRO: no differences	Neither Mesh Neither Neither	Pelvic pain: 14.8% vs. 10.7% (N/A)	N/A
Rudnicki, 2014	POP-Q<2: 88.1% vs. 39.8%* PRO: no differences	Mesh Neither	Mesh exposure: 13.3% vs. 0% De novo dyspareunia: 2.7% vs. 0%* De novo SUI: 5.3% vs. 0%* UTI: 6.7% vs. 13.3%*	NTR NTR NTR Mesh
Vollebregt, 2011	POP-Q<2: 91% vs. 41%* Reoperation for POP or mesh exposure: 11% vs. 7% (ns) De novo rectocele: 23% vs. 10% (ns) Feeling of bulge: 9% vs. 9% Visible bulge: 11% vs. 7% (ns)	Mesh Neither Neither Neither Neither	Mesh exposure: 4% vs. 0% De novo dyspareunia: 15% vs. 9% (ns)	NTR Neither
Carey, 2009	POP-Q<2: 81.0% vs. 65.6% (ns) Awareness of prolapse: 4.9% vs. 11.3% (ns) PRO: no differences	Neither Neither Neither	Mesh exposure: 5.6% vs. 0% De novo dyspareunia: 16.7% vs. 15.2% (ns)	NTR Neither
Lopes, 2010	POP-Q Ba>0: 57.1% vs. 43.8% (ns) QoL: no differences	Neither Neither	Mesh erosion: 35.7% vs. 0% (N/A) De novo UI: 0% vs. 6.3% (N/A)	NTR Neither
Delroy, 2013	POP-Q<2: 82.5% vs. 56.4%* QoL: no differences	Mesh Neither	Mesh extrusion: 5% vs. 0% (ns) UTI: 20% vs. 13.8% (ns) Dyspareunia: 5% vs. 10.2% (ns) Voiding dysfunction: 2.5% vs. 0% (ns) Urinary retention: 2.5% vs. 5.1% (ns)	NTR Neither Neither Neither Neither

Table A7. Randomized Controlled Trials with One Year Follow-up: Main Results				
Author, Year	**Effectiveness Results Mesh vs. NTR (statistical significance)**	**Favors**	**Safety Results Mesh vs. NTR (statistical significance)**	**Favors (based on statistical significance)**
Sivaslioglu, 2008	POP-Q<2: 91% vs. 72%* P-QOL: mesh group improved in more domains than NTR group	Mesh Mesh	Mesh erosion: 6.9% vs. 0% De novo dyspareunia: 4.6% vs. 0% (N/A) De novo SUI: 0% vs. 7% (N/A)	NTR Neither Neither
Nguyen, 2008	POP-Q Aa and Ba <1: 87% vs. 55%* QoL: no differences	Mesh Neither	Mesh extrusion: 5% vs. 0% (ns) De novo dyspareunia: 9% vs. 16% (N/A) UTI: 11% vs. 18% (ns) Urinary retention: 5% vs. 5% (ns)	NTR N/A Neither Neither
Altman, 2011	Composite outcome (POP-Q<2 and no bulging): 60.8% vs. 34.5%* POP-Q<2: 82.3% vs. 47.5%* Bulging: 24.6% vs. 37.9%* Sexual function (PISQ-12): no differences	Mesh Mesh Mesh Neither	Mesh exposure requiring surgical intervention: 3.2% De novo SUI: 12.3% vs. 6.3%*	NTR NTR
Milani, 2011	Sexual function (PISQ-12): no differences between groups; however there was no improvement in mesh arm, vs. improvement in NTR arm	Neither NTR	N/A	
Ek, 2013	Persistent lateral defect: 2.4% vs. 34.4%* POP-Q Ba≥0: 6.9% vs. 41.7%* UDI: no differences	Mesh Mesh Neither	N/A	
Halaska, 2012	Recurrence: 16.9% vs. 39.4%* QoL: no differences except in improvement of bowel symptoms	Mesh Neither	Mesh exposure: 20.8% De novo SUI: 35.1% vs. 25.4% (ns) Dyspareunia: 8.0% vs. 3.7% (ns) Pelvic pain: 8.1% vs. 5.5% (ns)	NTR Neither Neither Neither

Table A7. Randomized Controlled Trials with One Year Follow-up: Main Results				
Author, Year	**Effectiveness Results Mesh vs. NTR (statistical significance)**	**Favors**	**Safety Results Mesh vs. NTR (statistical significance)**	**Favors (based on statistical significance)**
dos Reis Brandao da Silveira, 2015	POP-Q Ba ≤0: 86.4% vs. 70.4%* POP-Q Bp ≤0: 97.7% vs. 91.4% (ns) POP-Q C ≤0: 92% vs. 84% (ns) PQoL: greater improvement in mesh group Reoperation for POP or mesh exposure: 7.9% vs. 3.7% (N/A) Recurrence: 2.3% vs. 3.7% (ns)	Mesh Neither Neither Mesh NTR Neither	Mesh extrusion: 20.5% vs. 7.4%* Dyspareunia: 3.4% vs. 6.2% (ns) Pain: 2.3% vs. 8.6% (ns)	NTR Neither Neither
Withagen, 2012; Withagen, 2011	POP-Q≥2: 9.6% vs. 45.2%* Subjective improvement (PGI): 81% vs. 80% (ns) De novo POP-Q≥2 in untreated compartments: 47% vs. 17%*	Mesh Neither NTR	Mesh exposure: 16.9% De novo dyspareunia: 8% vs. 10% (ns) De novo SUI: 10% vs. 9% (ns)	NTR Neither Neither
Svabik, 2014	Failure (POP-Q Ba, C, or Bp at hymen or below): 2.8% vs. 64.7%* POPDI, PISQ-12: no difference	Mesh Neither	De novo SUI: 36.1% vs. 8.8%* Dyspareunia: 5.6% vs. 2.9% (N/A)	NTR N/A
de Tayrac, 2013	POP-Q Ba<-1: 89% vs. 64%* Recurrence: 31.3% vs. 52.2%* QoL: no differences Satisfaction: 96% vs. 92% (ns) Repeat surgery for POP or AE: 10.7% vs. 13.9% (ns)	Mesh Mesh Neither Neither Neither	Erosion: 9.5% De novo dyspareunia: 23.1% vs. 7.1% (N/A) De novo SUI: 12% vs. 11% (ns)	NTR N/A Neither

Table A7. Randomized Controlled Trials with One Year Follow-up: Main Results				
Author, Year	**Effectiveness Results Mesh vs. NTR (statistical significance)**	**Favors**	**Safety Results Mesh vs. NTR (statistical significance)**	**Favors (based on statistical significance)**
Shveiky, 2012; Sokol, 2012[a]	POP-Q <2: 37.5% vs. 30.3% (ns) Recurrence: 62.5% vs. 67.7% (ns) Feeling of Bulge: 3.8% vs. 9.1% (ns) Reoperation for POP: 9.4% vs. 0% (ns) Reoperation for POP or mesh erosion: 15.6% vs. 0%*	Neither Neither Neither Neither NTR	Mesh exposure: 15.6% vs. 0%* De novo dyspareunia: 9.1% vs. 21.4% (ns) De novo SUI: 30.8% vs. 15.8% (ns)	NTR Neither Neither
Tamanini, 2013a; Tamanini, 2013b	POP-Q Ba≤2: greater improvement seen in mesh arm POP-Q <2: 83.7% vs. 55.5%* QoL: no differences Lower urinary tract symptoms (ICIQ-UI, OAB-V8): no differences	Mesh Mesh Neither Neither	Mesh exposure: 9.3% Dyspareunia: 2.3% vs. 0% De novo SUI: 0% vs. 1.8%*	NTR N/A Mesh
Glazener, 2017a; Glazener, 2017b	<u>Synthetic vs. NTR</u> POP-Q 2b, 3, or 4: 16% vs. 14% POP-SS>0: 85% vs. 83% (ns) Reoperation for POP: 3% vs. 2% (ns) QoL: no differences	 Neither Neither Neither	<u>Synthetic vs. NTR</u> Mesh complications: 7% vs. <1%	 NTR
	<u>Biologic vs. NTR</u> POP-Q 2b, 3, or 4: 18% vs. 16% POP-SS>0: 82% vs. 83% (ns) Reoperation for POP: 3% vs. 2% QoL: no differences	 Neither Neither Neither	<u>Biologic vs. NTR</u> Mesh complications: <1% vs. <1%	 N/A
Lamblin, 2014	POP-Q≤1: 100% vs. 88.2% (ns) Feeling of bulge: 6% vs. 3% (ns) QoL: no differences	Neither Neither Neither	Mesh erosion: 3% UTI: 3% vs. 3% (ns) Urinary retention: 0% vs. 6%	NTR

*Statistically significant between-group difference; ns=not statistically significant; N/A=not available (no statistical comparison performed)

[a]Study enrollment was prematurely halted due to high mesh exposure rate.

Table A8. Randomized Controlled Trials with Two Years Follow-up: Main Results				
Author, Year	**Effectiveness Results Mesh vs. NTR (statistical significance)**	**Favors**	**Safety Results Mesh vs. NTR (statistical significance)**	**Favors (based on statistical significance)**
Glazener, 2017a; Glazener, 2017b	<u>Synthetic vs. NTR</u> POP-Q 2b, 3, or 4: POP-SS>0: 85% vs. 82% (ns) QoL: no differences	 Neither Neither Neither	<u>Synthetic vs. NTR</u> Mesh complications: 6% vs. <1%	 NTR
	<u>Biologic vs. NTR</u> POP-Q 2b, 3, or 4: POP-SS>0: 82% vs. 81% (ns) QoL: no differences	 Neither Neither Neither	<u>Biologic vs. NTR</u> Mesh complications: <1% vs. <1%	 Neither
Menefee, 2011	POP-Q≥2: 18% (synthetic) vs. 46% (porcine) vs. 58% (NTR) Composite failure (POP-Q, bulge): 4% (synthetic) vs. 12% (porcine) vs. 13% (NTR) QoL: no differences	Synthetic Neither Neither	Mesh erosion: 14% (synthetic) vs. 4% (porcine) vs. 0% (NTR) (ns) De novo dyspareunia: 7.1% vs. 7.7% vs. 12.5% (ns)	Neither Neither
Minassian, 2014	POP-Q≥2: 32% vs. 40% (ns) Satisfaction: 88% vs. 73% (ns) QoL: no differences	Neither Neither Neither	N/A	N/A
Madhuvrata, 2011	Subjective success (POPSS, no residual symptoms): 24% vs. 28% (ns) QoL: no differences Satisfaction: 87.0% vs. 84% (ns)	Neither Neither Neither	Mesh removal: 6.2% Dyspareunia: 33% vs. 25% (ns)	NTR Neither
El-Nazer, 2012	POP-Q Aa, Ba, Ap and Bb=0: 80% vs. 35%* Recurrence: 5% vs. 15% (ns) Bulge: 5.3% vs. 26.7% (N/A)	Mesh Neither N/A	Mesh erosion: 5% De novo dyspareunia: 0% vs. 8.3% (N/A) De novo SUI: 0% vs. 20% (ns) UTI: 15% vs. 10% (ns)	NTR N/A Neither Neither

Table A8. Randomized Controlled Trials with Two Years Follow-up: Main Results				
Author, Year	**Effectiveness Results Mesh vs. NTR (statistical significance)**	**Favors**	**Safety Results Mesh vs. NTR (statistical significance)**	**Favors (based on statistical significance)**
Dias, 2016	POP-Q Ba<-1: 74.4% vs. 51.2%* Satisfaction: 97.3% vs. 81.8%* Bulge: 5.4% vs. 9% (N/A)	Mesh Mesh N/A	Mesh exposure: 13.5% De novo dyspareunia: 5.4% vs 12.1% (N/A) De novo SUI: 0% vs. 14.3% (N/A)	NTR N/A N/A
Tamanini, 2015	POP-Q Ba≤-1: 95.2% vs. 86% (ns) QoL: no differences	Neither Neither	Mesh exposure: 16.4%	NTR
Lamblin, 2014	POP-Q≤1: 100% vs. 84.4%* Feeling of bulge: 6% vs. 6% (ns) QoL: no differences	Mesh Neither Neither	Mesh erosion: 6% De novo dyspareunia: 3% vs. 2.9% (N/A)	NTR N/A
Maher, 2011	POP-Q<2: 43% vs. 77%* Reoperation: 22% vs. 5%* Satisfaction: higher for LSC	LSC LSC LSC	Mesh erosion: 9% vs. 2%	LSC
Damiani, 2016	POP-Q<2: 81% vs. 72.9%* De novo POP: 9% vs. 1% (N/A)	Mesh N/A	Mesh exposure: 3.4% De novo dyspareunia: 15.5% vs. 5% (N/A) De novo SUI: 15.5% vs. 8.4% (N/A)	NTR N/A N/A

*Statistically significant between-group difference; ns=not statistically significant
LSC=Laparoscopic sacrcolpopexy

Table A9. Randomized Controlled Trials with Three Years Follow-up: Main Results				
Author, Year	**Effectiveness Results Mesh vs. NTR (statistical significance)**	**Favors**	**Safety Results Mesh vs. NTR (statistical significance)**	**Favors (based on statistical significance)**
Rudnicki, 2016	POP-Q<2: 91.4% vs. 41.2%* PFIQ-7, PFDI-20, PISQ: no difference Bulging: 16% vs. 32%*	Mesh Neither Mesh	Mesh exposure: 14.7% vs. 0% (N/A) De novo dyspareunia: 0% vs. 0% (N/A)	NTR Neither
Nieminen, 2010	Recurrence: 13% vs. 41%* Reoperation: 11% vs. 18% POP-Q<2: 91% vs. 65%	Mesh Mesh Mesh	Mesh exposure: 19% vs. 0% (N/A) Dyspareunia scale: no difference	NTR Neither
Gutman, 2013	POP-Q<2: 45% vs. 43% (ns) No prolapse beyond hymen: 85% vs. 71% (ns) No bulge: 92% vs. 81% (ns) Reoperation: 13% vs. 0% (ns) Improvement: 90% vs. 86%	Neither Neither Neither Neither Neither	Mesh exposure: 15.6% vs. 0%[a] De novo dyspareunia: 8% vs. 4% (ns) De novo SUI: 12% vs. 7.7% (ns)	NTR Neither Neither
Dahlgren, 2011	Recurrence (anterior): 62% vs. 57% (ns) Improvement: 84% vs. 85%	Neither Neither	Mesh erosion: 4.4% vs. 0%	NTR

*Statistically significant between-group difference; ns=not statistically significant

[a]Study enrollment was prematurely halted due to high mesh exposure rate.

Prospective Cohort Studies

Table A10. Prospective Cohort Studies for Uphold or Uphold LITE, Xenform, or Restorelle or Restorelle DirectFix Anterior meshes						
Author, Reference	**Repair Type, n**	**Material**	**Compartment**	**Endpoint**	**12 Month Results**	**Device Evaluated (trade name, manufacturer)**
Morcos, 2018[41]	Mesh Study #1 Single Center n=112	Synthetic	Apical with or without concomitant anterior	POP-Q Stage 0-1 Surgical data	POP-Q: 94% Reoperation rate: 1% Serious complications: 0% SUI: 2.7%	Uphold, Boston Scientific[a]
	Mesh Study #2 Multi Center n=203	Synthetic	Apical with or without concomitant anterior	POP-Q ≤1 Surgical data	POP-Q: 97% Reoperation rate: 1.8% Serious complications: 4.3% SUI: 6%	
Nicita, 2018[44]	Mesh n=66	Synthetic	Anterior/apical	POP-Q ≤2 PQoL	POP-Q: 92.5% PQoL improved since baseline De novo dyspareunia: 17.6% De novo SUI: 0%	Restorelle, Coloplast
Gutman, 2017[39]	Mesh n=76	Synthetic	Anterior/apical	Composite anatomic and symptomatic cure	Cure: 74% Mesh exposure: 6.6% UTI: 25%*	Uphold and Uphold Lite, Boston Scientific[b,c]
	Native Tissue Repair n=74	N/A	Anterior/apical	Composite anatomic and symptomatic cure	Cure: 72% UTI: 11%	N/A
Rahkola-Soisalo, 2017[40]; Altman, 2016[42]	Mesh n=207	Synthetic	Apical with or without Anterior	POP-Q ≤1 Symptom Relief QoL improvement Dyspareunia worsening Sexual function worsening	POP-Q: 94% Symptom: 91% QoL: 64.8% Dyspareunia: 8.1% Sexual function: 66% Serious complications: 4.3%	Uphold[a]

Table A10. Prospective Cohort Studies for Uphold or Uphold LITE, Xenform, or Restorelle or Restorelle DirectFix Anterior meshes						
Author, Reference	**Repair Type, n**	**Material**	**Compartment**	**Endpoint**	**12 Month Results**	**Device Evaluated (trade name, manufacturer)**
	Mesh n=137	Synthetic	Apical alone	Prolapse related bother	OR=2.1 (1.01-4.3) compared to apical with anterior	
	Mesh n=64	Synthetic	Apical with Anterior	Prolapse related bother	(ref)	
Jirschele, 2015[43]	Mesh n=99	Synthetic	Anterior or anterior/apical	Composite outcome (POP-Q and feeling of bulge) Reoperation Mesh exposure	Composite outcome: 97.7% Reoperation: 7.5% Mesh exposure: 6.5%	Uphold, Boston Scientific[a,c]
Fayyad, 2014[45]	Mesh n=70	Synthetic	Anterior or anterior/apical	POP-Q ≤1 Reintervention for prolapse Mesh-related complications	POP-Q: 95.7% Reintervention: 8.5% Complications: 2.9% (1 post-menopausal bleeding, 1 dyspareunia)	Restorelle, Coloplast
Goldstein, 2010 [46]	Mesh n=45	Biologic	Anterior and posterior	POP-Q PFDI-20 PISQ-12 Mesh-related complications	POP-Q: 74% at stage 0 or 1 PFDI-20: 72% improvement from baseline PISQ-12: maintained from baseline No mesh related erosion or pain lasting beyond 30 days	Xenform

*Statistically significant difference for mesh vs. non-mesh groups

[a]Study was supported with grant or support from manufacturer

[b]Manufacturer donated devices to study

[c]Authors reported/disclosed other relationship with manufacturer such as research, consulting, etc.

Appendix III – Methods and Limitations of MDR Database Search

The methods for the MDR database search are summarized below.

Device Type: mesh placed transvaginally in the anterior vaginal compartment to treat POP

Product Code: OTP (mesh, surgical, synthetic, urogynecologic, for pelvic organ prolapse, transvaginally placed)
PAI (mesh, surgical, non-synthetic, urogynecologic, for pelvic organ prolapse, transvaginally placed)
FTL (mesh, surgical, polymeric)
FTM (mesh, surgical)

Note: OTP and PAI were created in 2012, and prior to that FTL and FTM were used for all surgical mesh.

Date Range: January 1, 2008 – September 30, 2018

Company: all

Device: all

Analyses: Total number of MDRs per year for all transvaginal prolapse mesh devices

Total number of deaths, injuries, and device malfunctions for all transvaginal prolapse mesh devices

List of top 10 injury reports (number and rate) for all transvaginal prolapse mesh devices

Search Strategy: Search narratives for the following terms to help ensure we are only including anterior transvaginal prolapse procedures:

- Prolapse
- Cystocele
- Anterior repair
- Apical repair
- Pelvic floor
- Bladder prolapse
- Vagina
- Vaginal
- Uterus
- Uterine

Each year, the FDA receives several hundred thousand MDRs of suspected device-associated deaths, serious injuries and malfunctions. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. Medical device manufacturers, importers, and device user facilities are required to report known adverse events as part of the general controls, and health care professionals, patients, and consumers are encouraged

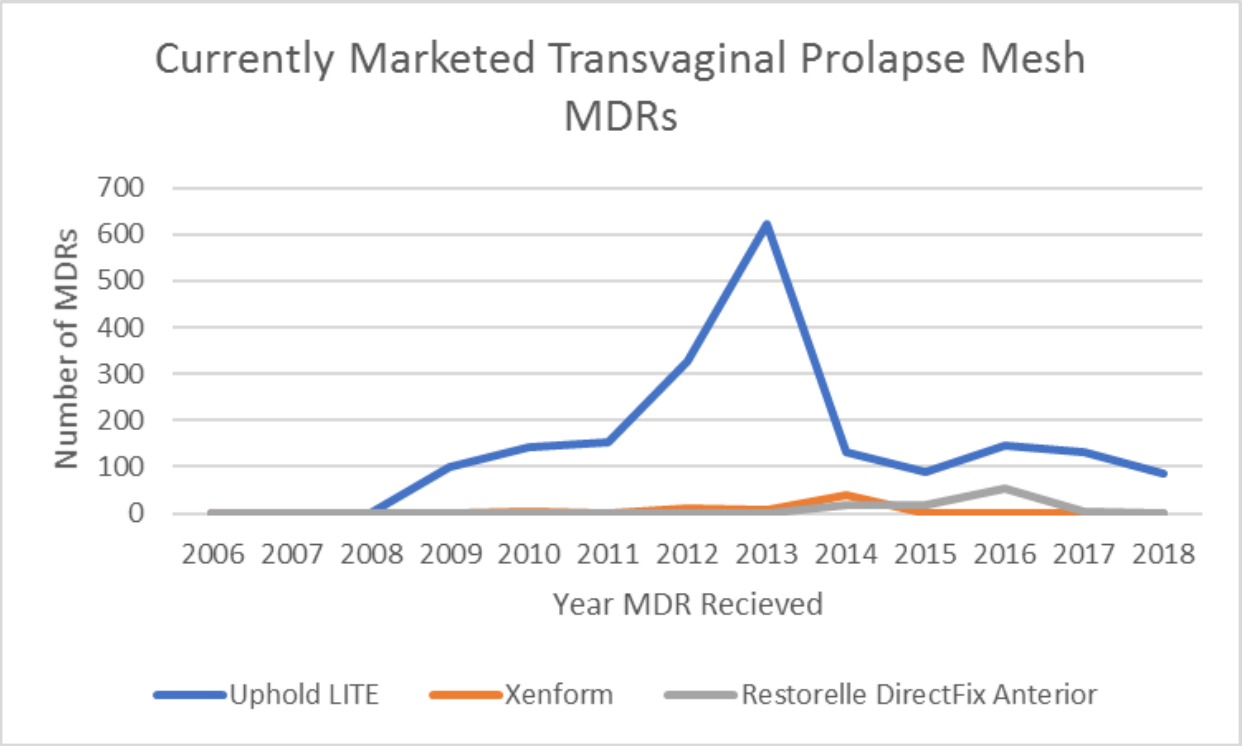
to voluntarily report adverse events. MDRs provide a qualitative snapshot of adverse events for a specific device or device type when they are being used in a “real world” setting/environment. However, it is a passive surveillance system, and therefore MDRs can contain incomplete, inaccurate, untimely, unverified, or biased data. The incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. As such, MDRs comprise only one of the FDA's several important postmarket surveillance data sources.

Other limitations of MDRs include but are not necessarily limited to:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MDR data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

Appendix IV – MDRs Per Year and Top Ten Patient Problems for Currently Marketed Devices

The following figure depicts the MDRs per year for the three currently marketed devices indicated for anterior repair of POP transvaginally.



The following table provides the top ten patient problems for the Boston Scientific Uphold LITE. In the timeframe from 2006-2018, there were 1,987 MDRs for this device. Please note that the MDR count for Uphold LITE may include reports for Uphold.

	Patient Problem	Count
1	Pain	299
2	Erosion	215
3	Device fragments in patient	107
4	Infection	72
5	Urinary Retention	63
6	Infection, Urinary Tract	46
7	Incontinence	37
8	Perforation	22
9	Injury	16
10	Nonresorbable materials, unretrieved in body	15

Note: This list is not all inclusive and more than one patient problem code is often found in a single MDR.

The following table provides the top ten patient problems for the Boston Scientific Xenform. In the timeframe from 2006-2018, there were 67 MDRs for this device.

	Patient Problem	Count
1	Pain; Pain, Abdominal; Discomfort	53
2	Incontinence	40
3	Injury	40
4	Infection	40
5	Erosion	35
6	Therapeutic Response, Decreased	33
7	Organ(s), Perforation Of	30
8	Tissue Damage	30
9	Vaginal Mucosa Damage	30
10	Hemorrhage	8

Note: This list is not all inclusive and more than one patient problem code is often found in a single MDR.

The following table provides the top ten patient problems for the Coloplast Restorelle DirectFix Anterior. In the timeframe from 2006-2018, there were 96 MDRs for this device. Please note that the MDR count for Restorelle DirectFix Anterior may include reports for Restorelle.

	Patient Problem	Count
1	Pain	56
2	Prolapse	31
3	Incontinence	28
4	Infection	24
5	Infection, Urinary Tract	21
6	Scarring	17
7	Erosion	16
8	Hemorrhage	15
9	Complaint, Ill-Defined	12
10	Urinary Retention	11

Note: This list is not all inclusive and more than one patient problem code is often found in a single MDR.