MASTER CLASS

To Mesh or Not to Mesh?

CHARLES E. MILLER, M.D.

On July 13, 2011, the Food and Drug Administration issued a safety communication, "Update on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse," intended for health care providers and patients. Previously, on Oct. 20, 2008, the FDA issued a Public Health Notification and Additional Patient Information statement on serious complications associated with surgical mesh placed transvaginally to treat pelvic organ prolapse (POP) and stress urinary incontinence (SUI).

In the July 2011 bulletin, the FDA stated that "serious complications associated with surgical mesh for transvaginal repair of pelvic organ prolapse are not rare. … Furthermore, it is not clear that transvaginal pelvic organ prolapse repair with mesh is more effective than traditional nonmesh repair in all patients with pelvic organ prolapse and it may expose patients to greater risk."

In its bulletin, the FDA noted a marked increase in reported adverse events related to surgical mesh devices used to repair POP and SUI in reporting years 2005-2007 vs. 2008-2010. The most frequent complications reported to the FDA regarding transvaginal mesh placement for POP were mesh erosion through the vagina, pain, infection, bleeding, dyspareunia, organ perforation, and urinary problems. Also noted were recurrent prolapse, neuromuscular problems, vaginal scarring/shrinkage, and emotional problems. Moreover, men may experience irritation and pain to the penis during intercourse secondary to exposed mesh.

The FDA also reported on its systematic review of literature from the period of 1996-2011 to evaluate transvaginal mesh safety and effectiveness. In particular, the FDA noted the following:

- Potential for additional risk when mesh is utilized in POP surgery.
- Greater rate of complications in POP surgery when mesh placed transvaginally, rather than transabdominally.
- No advantage of mesh for either apical or posterior repair, compared with traditional surgery without mesh.
- Although mesh may be beneficial anatomically for anterior repair, symptoms may not improve over conventional anterior repair.

The FDA then went on to make recommendations to both health care workers and patients.

Health care workers are advised to obtain specialized training for each mesh placement technique. Mesh should be considered only after weighing the risks and benefits, as well as considering other nonsurgical and surgical options including nonmesh and transabdominal mesh techniques.

Patients must be made aware that surgical mesh is a permanent implant, which may make future surgical repair more challenging.

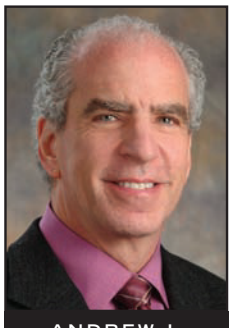
Moreover, mesh may place the patient at greater risk for requiring additional surgery for the development of additional complications. Removal of mesh when complications arise may involve multiple surgeries and may negatively impact the patient's quality of life. Complete removal of the mesh may not be possible, and even if it is removed, symptoms may continue. Patients also must realize the lack of long-term data.

To understand how this latest FDA bulletin will impact the surgical treatment of POP and SUI, I have called upon Dr. Andrew I. Brill, director of minimally invasive surgery and reparative pelvic surgery at California Pacific Medical Center, San Francisco. He also is a voting member of the FDA Obstetrics and Gynecology Device Panel. Prior to moving to the Bay Area in 2006, Dr. Brill was professor of obstetrics and gynecology at the University of Illinois at Chicago, where he directed one of the first accredited fellowships in minimally invasive gynecology. Dr. Brill is a past president of both the AAGL and the board of directors of the AAGL/Society of Reproductive Surgeons Fellowship in Minimally Invasive Gynecology. Widely recognized in the United States and abroad as a leading educator in the field of minimally invasive gynecology, Dr. Brill is a frequent lecturer and telesurgeon, and he continues to be a regular contributor to peer literature and textbooks, having coauthored a leading textbook and more than 50 articles and book chapters. ■

DR. MILLER *is clinical associate professor at the University of Illinois at Chicago, present-elect of the International Society for Gynecologic Endoscopy (www.isge.org), and a past president of the AAGL (www.aagl.org). He is a reproductive endocrinologist and minimally invasive gynecologic surgeon in private practice in Naperville, Ill., and Schaumburg, Ill.; the director of minimally invasive gynecologic surgery at Advocate Lutheran General Hospital, Park Ridge, Ill.; and the medical editor of this column. Dr. Miller said he is a consultant to Ethicon Women's Health and Urology and to Boston Scientific.*

The Hoopla Over Mesh: What It Means for Practice

The Food and Drug Administration's warning last summer of the risks associated with transvaginal placement of mesh for repair of pelvic organ prolapse and stress urinary incontinence – and its overall, ongoing review of how mesh products are cleared for use – have changed the climate for ob.gyns. and patients. It has upped the ante for comprehensive patient counseling and brought to the fore the fact that pelvic floor repair is a combination of art, science, judgment, skill, training, and experience.



ANDREW I. BRILL, M.D.

In July 2011, the FDA issued a "safety communication" to physicians and patients, which was based on an analysis of adverse event reports and a systematic literature review, warning that the transvaginal placement of mesh to treat pelvic organ prolapse (POP) appears to be riskier than traditional repairs without any evidence of greater effectiveness. While an earlier FDA notice issued in 2008 had said in essence that there *may be* a problem with transvaginal mesh, the most recent warning said there *is* a problem – that serious complications associated with surgical mesh used for transvaginal repair of POP are not rare.

The agency made a distinction between apical and posterior repair, and anterior repair, concluding that there is no evidence that either apical or posterior repair done with mesh provides any added benefit compared with traditional surgery without mesh.

With regard to anterior repair, the FDA concluded that mesh augmentation may provide an anatomic benefit compared with traditional nonmesh repair, although this anatomic benefit may not necessarily lead to better symptomatic results.

The FDA also reviewed all types of midurethral sling (MUS) devices used to treat stress urinary incontinence (SUI), grouping retropubic and transobturator slings as first-generation and mini-slings as second-generation devices.

Whereas these devices were deemed to be as effective as or better than traditional repairs, the FDA stated its concerns about the potential for long-term problems including mesh erosion and pelvic pain. Moreover, the agency stated the need for more data to better evaluate mini-slings for comparative efficacy and complications.

More broadly, the FDA is reevaluating how transvaginal mesh products should be regulated and brought to market. Unlike other devices that are widely used by ob.gyns., not one of the pelvic floor mesh kits for POP or midurethral slings for SUI has been evaluated by way of an independent, FDA-mandated randomized clinical trial. This is because transvaginal meshes are currently classified as class II devices and, as such, have been cleared for market by the less rigorous 510(k) notification process rather than a more rigorous premarket approval (PMA) process.

While the FDA considers the 510(k) pathway still suitable for MUS devices used to treat SUI, the agency is taking a harder look at transvaginal mesh used to repair POP and has recommended reclassification of these devices into class III. This switch would require the more onerous PMA process and allow the FDA to require clinical trials comparing procedures that involve mesh with those in which mesh is not used.

How the FDA Regulates Devices

That transvaginal mesh devices are embroiled in a broader and ongoing controversy over how best to regulate or approve medical devices is important to understand. Innovation and potential market share continue to drive a steady stream of new medical devices for gynecologic surgery.

Until 36 years ago there was no federal regulation of medical devices. The Medical Device Amendments of 1976 established three device classes, based on risk levels and the ability of postmarketing controls to manage those risks. The law then identified pathways, based largely on this classification system, for bringing devices to the market.

Class I devices are generally those for which general postmarketing controls such as good manufacturing processes and record keeping are deemed sufficient to provide reasonable assurance of safety and effectiveness. Devices in class II, which are "moderate risk," need special controls such as performance standards and postmarketing surveillance to provide reasonable assurance of safety and effectiveness. In class III are life-sustaining or life-supporting "high-risk" devices that cannot be placed in class I or II because there is insufficient information to establish requisite assurance with postmarketing controls.

While FDA-approved randomized and controlled clinical trials are required for class III devices as part of the standard PMA process, class II devices are cleared for the market based on the substantially less rigorous 510(k) Premarket Notification Program process, which requires manufacturers to demonstrate safety and effectiveness by proving "substantial equivalence" to another device that is already cleared by the FDA based on intended use and product design.

Whereas clinical data are not required, this review of substantial equivalence requires labeling and performance data, including material safety, mechanical performance, and animal testing. Approval of the first surgical mesh for

Continued on following page

Continued from previous page

repair of POP was judged to be substantially equivalent to surgical mesh used for hernia repair.

In recent years there has been growing concern about this process of clearing medical devices based simply on substantial equivalence with a predicate. New products should not necessarily be assumed to have equal or improved safety and efficacy. The Institute of Medicine weighed in this past summer with a report on the 510(k) clearance process, calling it flawed in its ability to provide determinations about each device's safety and effectiveness.

Overall, transvaginal mesh repair of POP is best suited to women who are high risk due to medical conditions and in those with recurrent prolapse, particularly of the anterior compartment.

The future of transvaginal mesh products is now entangled in these concerns. Unlike devices for endometrial ablation and transcervical hysteroscopic sterilization, which are justifiably classified as class III devices, all transvaginal mesh devices to date have been cleared as class II devices.

Since 2001, the FDA has cleared via the 510(k) approval process more than 100 synthetic mesh devices or kits indicated for POP repair, and more than 75 mesh devices to treat SUI (including 7 second-generation mini-slings), using the 510(k) notification process. None of the clearances were based on clinical data.

While there have indeed been some randomized clinical trials (in its recent review, FDA officials reported having looked at 22 randomized controlled trials and 38 observational studies on the use of mesh to treat POP), many of these trials have been designed and conducted with industry sponsorship.

The FDA typically calls upon its advisory panels to provide independent expert advice when specific issues or problems arise and when regulatory decisions need to be made both before and after approval of medical devices.

After issuing its "safety communication" last July, the FDA convened the Obstetrics and Gynecology Devices Advisory Panel in September to make recommendations regarding the safety and effectiveness of surgical mesh for repair of POP and SUI. Ironically, transvaginal mesh devices had previously been regulated by the FDA's Plastic Surgery Devices Panel.

The 2-day public hearing included presentations regarding adverse events and effectiveness of transvaginal mesh for POP and then SUI by FDA staff reviewers, key medical organizations, related industry as a consortium, and public advocacy groups as well as personal testimony by patients having undergone these procedures.

After hearing the testimony and an exhaustive discussion, the majority of panel members supported reclassifying mesh devices for POP from class II to class III. On the other hand, while the majority did not recommend the reclassification of devices for SUI, the panel concurred that more clinical data was warranted to establish the safety and efficacy of second-generation mini-slings.

The FDA's final regulatory decisions will slowly evolve as the issues of safety and effectiveness are balanced with reducing the burden for industry and continuing to foster a hospitable climate for medical innovation.

Adverse Event Reports

The FDA's safety communication released in July, which updated the 2008 FDA Public Health Notification, was generated by continuing concerns raised by rising reports of adverse events as well as concern voiced by the American Urogynecologic Society.

The adverse event reports have been compiled via the FDA's Manufacturer and User Facility Device Experience (MAUDE) database, which collects both mandated reporting by manufacturers and voluntary reports by physicians, patients, and any interested party. It is presumed that complications are generally underreported.

From 2008 to 2010, the FDA received 2,874 adverse event reports associated with urogynecologic mesh – about three times the number of reports filed from 2005 to 2007. Of these, 1,503 were associated with products for POP, and 1,371 were associated with products for SUI.

It is unclear, of course, how much of this increase reflects an increase in actual adverse events and how much stems from the increased use of mesh, an increased awareness of adverse events, possible duplication of reporting, and other factors that are inherent limitations of the reporting process. Moreover, the complication rate is not known because the total number of adverse events and the total number of implanted delivery systems are not known.

Erosion, exposure, and extrusion continue to be the most frequent and concerning adverse events associated with mesh used for POP and SUI. With its more recent review, the FDA has new concerns about the delayed appearances of erosion and mesh exposure. While there are few treatment cohorts to evaluate after 36 months, there have been a number of reports of long-term adverse outcomes – some at time points up to 60 months post procedure.

Moreover, the FDA is concerned about the risk for later development of dyspareunia and new pelvic pain from mesh contraction, retraction, vaginal shrinkage, and subsequent reoperation – problems not identified or flagged when the agency completed its last comprehensive review before issuing the 2008 notification.

Current State of Transvaginal Mesh

In the most recent safety communication, the FDA instructs patients to be aware of the risks associated with surgical mesh for transvaginal repair of POP and SUI. It warns patients that having transvaginal mesh surgery may increase their risk of needing additional surgery due to mesh-related complications, and it advises patients to ask their surgeons about all POP treatment options.

See related story on page 16.

The alert also tells patients to notify their physicians regarding vaginal or pain symptoms after surgery with transvaginal mesh, and to let their health care providers know they have implanted mesh – advice that, in and of itself, can create fear. Any patient doing diligent research will see the statement and related discussion.

In issuing the communication, the FDA has set the bar at a higher level of expectation for patient counseling and informed consent.

While the FDA does not regulate the practice of medicine by regulating how or which physicians can use devices, the agency indirectly is regulating the use of transvaginal mesh devices through its alerts.

And without question, the probability for medical-legal conflict has been substantially heightened. Propelled by the FDA warnings, a cursory Internet search for "pelvic mesh lawyers" or "vaginal mesh lawsuit attorneys" yields a list of firms encouraging free case reviews.

Patients should be counseled that transvaginal mesh procedures are considered innovative techniques for pelvic floor repair that demonstrate high rates of anatomic cure in shorter-term series.

Preoperative counseling should cover the following principles and guidelines:

- There are potential adverse sequelae of transvaginal mesh repairs.
- There are limited data comparing transvaginal mesh systems with traditional vaginal prolapse repairs or with traditional use of graft material in the form of augmented colporrhaphy and sacrocolpopexy.
- The placement of surgical mesh for POP by sacrocolpopexy for apical prolapse is a well established clinical practice and may result in lower rates of mesh complications.
- Transvaginal apical or posterior repair with mesh does not appear to provide any added benefit compared with traditional surgery without mesh.

The main role for mesh with POP repair is in the anterior compartment, where a higher risk of recurrence with traditional repairs has been documented.

Overall, transvaginal mesh repair of POP is best suited to women who are high risk due to medical conditions and in those with recurrent prolapse, particularly of the anterior compartment.

- The effectiveness of retropubic and transobturator suburethral slings for SUI has been demonstrated, while the safety and effectiveness of single-incision mini-slings is less well established.

Rather than the fault of the device or method, the failure or success of transvaginal mesh repairs may rely far more on the skill and judgment of the surgeon.

All surgery incorporates an intricate blend of art and science. We must be realistic in evaluating our skills, experience, and expertise in performing transvaginal mesh procedures.

Even in the best of circumstances, factors such as obesity, hypoestrogenism, advanced age, poor nutrition, extreme life activity, multiparity, Northern European descent, smoking, prior reparative surgery, and diabetes may reduce the success of transvaginal mesh procedures and increase complications.

While patient concerns will be heightened, the decision to perform a particular type of restorative or reparative surgery for POP, with or without mesh, should always favor reduced risk along with optimal and durable outcome that is both anatomic and functional in nature. And clinical decision making, as always, must be guided by our Hippocratic vow "primum non nocere"! ■

DR. BRILL *said he is a consultant and speaker for Ethicon Endosurgery, Gynecare, Conceptus, and Karl Storz.*

POP Adverse Events, 2005-2010

Rank	Type of event	Medical device reports
1	Erosion	528
2	Pain	473
3	Infection	253
4	Bleeding	124
5	Dyspareunia	108
6	Organ perforation	88
7	Urinary problems	80
8	Vaginal scarring/shrinkage	43
9	Neuromuscular problems	38
10	Recurrent prolapse	32

Note: Based on data from the FDA's Manufacturer and User Facility Device Experience (MAUDE) database.
Source: Dr. Brill

SUI Adverse Events, 2005-2010

Rank	Type of event	Medical device reports
1	Pain	479
2	Erosion	436
3	Infection	260
4	Urinary problems	220
5	Organ perforation	110
6	Recurrent incontinence	103
7	Bleeding	103
8	Dyspareunia	73
9	Neuromuscular problems	50
10	Vaginal scarring	22

Note: Based on data from the FDA's Manufacturer and User Facility Device Experience (MAUDE) database.
Source: Dr. Brill