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Commissioner
Food and Drug Administration
Department of Health and Human Services
WO 2200
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Silver Spring, MD 20993-0002

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Dear Drs. Hamburg and Shuren,

Public Citizen, a consumer advocacy group representing more than 225,000 members and supporters nationwide, hereby petitions the Food and Drug Administration (FDA), pursuant to the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 360f and 360h, and 21 C.F.R. §§ 10.30, 810, and 895, to immediately:

(1) ban the marketing of all currently available non-absorbable surgical mesh products specifically designed and labeled for transvaginal repair of pelvic organ prolapse (POP) — which were used in an estimated 67,500 surgical procedures

in the U.S. in 2010[*] — because these devices (a) offer no clinically significant benefits in comparison to surgical repairs for POP performed without placement of surgical mesh; and (b) have high rates of serious complications, many of which require additional surgical intervention and some of which are not amenable to surgical correction and result in permanent life-altering harm, therefore presenting "an unreasonable and substantial risk of illness or injury," the standard for the FDA to institute proceedings to ban a device under the device law, 21 U.S.C. § 360f and 21 C.F.R. § 895.21(a);

(2) order all manufacturers of non-absorbable surgical mesh products specifically designed and labeled for transvaginal repair of POP to recall these products; and

(3) require that any non-absorbable surgical mesh product specifically designed and labeled for transvaginal repair of POP that is proposed for marketing in the future be classified as a class III device and be approved for marketing only under a premarket approval application (PMA) that includes data from well-designed, prospective clinical trials that provide a reasonable assurance that the surgical mesh product is safe and effective.

I. BACKGROUND

A. Regulatory status of surgical mesh products for transvaginal repair of POP

A variety of surgical mesh products specifically designed for repair of POP are marketed in the U.S. Examples include the following:

- Gynecare Prolift Total, Anterior, and Posterior Pelvic Floor Repair Systems (Ethicon, Inc., Somerville, NJ)
- Gynecare Prolift +M Total, Anterior, and Posterior Pelvic Floor Repair Systems (Ethicon, Inc.)
- Gynemesh Prolene Soft Nonabsorbable Synthetic (Ethicon, Inc.)
- AMS Elevate Anterior and Apical Prolapse Repair System (American Medical Systems, Inc., Minnetonka, MN)
- Pinnacle Pelvic Floor Repair Kits (Boston Scientific Corp., Marlborough, MA)
- Avaulto Support System (C.R. Bard, Inc., Covington, GA)
- Polyform Synthetic Mesh (Proxy Biomedical, Ltd., Galway, Ireland)

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[*] Our estimate of 67,500 was calculated as follows: Based on data from surgical mesh manufacturers, the FDA reported that (a) in 2010 approximately 300,000 women in the U.S. underwent surgical procedures for POP repair, (b) approximately one-third of these POP surgeries used mesh (i.e., 100,000) and (c) approximately three-fourths of these mesh procedures were done transvaginally (i.e., 75,000). Assuming that 90% of these mesh procedures used non-absorbable mesh, the total number of transvaginal POP repair procedures using non-absorbable surgical mesh performed in the U.S. in 2010 was approximately 67,500.

These devices carry the FDA regulatory description of "surgical mesh" (see 21 C.F.R. § 878.3300[1]) and FDA product code FTL or FTM, are class II devices, and were reviewed by the FDA under the 510(k) premarket notification process.[2] The FDA regulations identify surgical mesh as "a metallic or polymeric screen intended to be implanted to reinforce soft tissue or bone where weakness exists. Examples of surgical mesh are metallic and polymeric mesh for hernia repair, and acetabular and cement restrictor mesh used during orthopedic surgery."[1]

These surgical mesh products generally have been cleared for marketing based solely on in vitro bench and/or animal testing to confirm that engineering specifications are met and that mesh material is biocompatible. Clinical trials in human subjects to assess the safety and efficacy of these devices generally have not been carried out prior to the FDA's clearance for marketing.[3]

B. Pelvic organ prolapse

POP involves the protrusion or descent of one or more of the pelvic organs into the vagina (or prolapse of the vaginal vault itself) due to weakness of or injury to the connective tissues and muscles that normally provide support to these organs.[4] POP is common and occurs in 40-50% of parous women (women who have given birth to a child) and in 6% of non-parous women.[4,5] The types of POP are classified according to the compartment or segment of the vagina affected and the organ that has prolapsed and include the following:[4,6]

- Anterior vaginal wall prolapse: cystocele (prolapse of the urinary bladder) and urethrocele (prolapse of the urethra)
- Posterior vaginal wall prolapse: rectocele (herniation of the rectum into the vagina)
- Enterocele (herniation of loops of small bowel into the vagina, usually occurring either apically or posteriorly)
- Uterine prolapse (prolapse of the uterus and cervix, or prolapse of the cervix alone in women who have had a supracervical hysterectomy)
- Prolapse of the vaginal vault (which occurs only after hysterectomy; this is sometimes referred to as apical prolapse)

Prolapse affecting the anterior vaginal wall (cystocele) is the most common type of POP.[7] In an individual patient, prolapse may involve more than one segment of the vagina simultaneously.[4]

The etiology of POP is multifactorial. Possible risk factors include pregnancy itself, parity, congenital or acquired connective tissue disorders or injuries, aging, hysterectomy, menopause, and factors associated with a chronic elevation in intra-abdominal pressure.[4,5]

Except in very rare cases, POP is not a life-threatening condition.[8] Most women with POP are asymptomatic.[5] However, in some women, POP causes symptoms that can

adversely impact the quality of life (QOL). These symptoms can include discomfort from vaginal bulging, a visible bulge or protrusion through the vaginal opening, pelvic pressure, sexual dysfunction, difficulty voiding or defecating (e.g., women may need to manually push the prolapse up in order to urinate or defecate), urinary incontinence, fecal incontinence, and backache.[4,8]

Women with symptomatic POP can be treated with surgical or non-surgical interventions. Conservative, non-surgical interventions include use of pessaries manually inserted into the vagina to provide support to the prolapsing organs, pelvic muscle exercises, and lifestyle interventions. While these interventions carry little risk, evidence supporting their efficacy is limited.[9,10]

Surgical interventions for POP include a wide variety of abdominal and vaginal surgical techniques. Among the most common procedures are anterior repair for anterior vaginal wall prolapse (anterior colporrhaphy) and posterior repair for posterior wall prolapse (posterior colporrhaphy). Most surgeries for POP (except apical prolapse or vaginal vault prolapse) are performed transvaginally.

It has become increasingly common for surgical mesh to be implanted as part of the operation for transvaginal POP repair with the intent of increasing the longevity of the repair.[3]

Surgical mesh materials can be divided into the following four major categories:[3]

- 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)
- Composite (i.e., a combination of any of the first three categories)

Most surgical mesh devices cleared for transvaginal surgical POP repair are composed of non-absorbable synthetic polypropylene.[3]

Based on data from manufacturers of surgical mesh, the FDA reported that approximately 300,000 women in the U.S. underwent surgical procedures to repair POP in 2010 and that approximately 75,000 of these procedures involved a transvaginal repair with implantation of surgical mesh.[3] (As noted in the footnote on page 2, assuming that 90% of these transvaginal POP repairs with mesh involved non-absorbable mesh, the total number of transvaginal POP repair procedures using non-absorbable surgical mesh performed in the U.S. in 2010 was approximately 67,500.)

II. STATEMENT OF GROUNDS

A. Use of surgical mesh for transvaginal POP repair provides no clinically significant benefit compared to repair without mesh using only native tissues

Most women who have POP on pelvic examination are asymptomatic and do not require any treatment. For symptomatic women with POP, the goal of treatment is relief of symptoms. Therefore, the assessment of the benefits of surgical procedures for transvaginal POP repair necessarily must focus on symptom relief rather than anatomic outcomes.

A review of the peer-reviewed scientific literature reveals that while transvaginal POP repair with mesh appears to result in less prolapse being detected on pelvic examination following surgery in comparison to non-mesh repair procedures using only native tissues, the use of mesh does not provide any better outcomes in terms of relief of symptoms and QOL measures, which ultimately are the clinically significant indicators for measuring treatment success for this condition. We outline here the series of randomized, controlled clinical trials and systematic reviews that have evaluated the efficacy and safety of POP repair procedures using surgical mesh.

Single-center, randomized, controlled trials of absorbable polyglactin 910 mesh

The two earliest studies evaluating the use of surgical mesh for transvaginal POP repair tested polyglactin 910 mesh (Ethicon, Inc.), an absorbable synthetic mesh.

The first such study, conducted by Sand et al, was a prospective, randomized, controlled clinical trial in 160 women with cystocele protruding to or beyond the vaginal hymen who were undergoing transvaginal anterior colporrhaphy (as well as posterior colporrhaphy in some cases), with or without an anti-incontinence procedure, between September 1995 and April 1999 at a single institution (the Evanston Continence Center, Evanston, IL).[11] The subjects were randomized to have the surgery with (n=80) or without (n=80) placement of absorbable polyglactin 910 mesh. The investigators excluded patients if they only had an anterior enterocele or only a paravaginal defect with no need for a central cystocele repair. Subjects also underwent correction of other prolapsed pelvic organs if present. At two, six, 12, and 52 weeks after surgery, subjects underwent assessments for pelvic anatomy, adverse effects, and continence and voiding function. The primary outcome variables were recurrent cystocele and rectocele at the mid-vaginal plane or beyond at 12 weeks and one year.

The key results of the Sand et al study were as follows:

- There was no significant difference in post-operative recurrence of cystocele or rectocele at 12 weeks.
- At one year, the difference in the recurrence of cystocele to the mid-vaginal plane (second-degree cystocele) was not statistically significant between the two study

groups (31% in non-mesh group versus 22% in mesh group, p=.20). The recurrence of cystoceles to the hymenal ring (third-degree cystocele) was statistically significantly higher in the non-mesh group than in the mesh group (11% versus 2.7%, p=0.04), as was the combined recurrence of second- and third-degree cystoceles (43% in the non-mesh group versus 25% in the mesh group, p=0.02).

- There was no difference in recurrence of rectoceles at one year for subjects undergoing such additional repair by posterior colporrhaphy.
- There were no adverse events noted from the polyglactin mesh during the trial.

The Sand et al study had several limitations, including the following:

- The study was conducted at a single site.
- The mesh tested was absorbable, whereas most transvaginal POP repair surgeries involving mesh placement today involve a synthetic, non-absorbable mesh.
- There was significant variation in the type of procedures subjects underwent.
- Seventeen subjects (seven in the mesh group and 10 in the non-mesh group) did not return for follow-up at one year and were not included in the analysis.
- Data on symptoms and QOL measures were not provided.
- Subjects and investigators were not blinded to study group assignment, which could have biased the assessment of the anatomic results.

The second study testing polyglactin 910 mesh, initially published by Weber et al[12] (with a subsequent reanalysis published by Chmielewski et al[13]), was a prospective, randomized, controlled clinical trial in 114 women with anterior vaginal wall prolapse who were undergoing transvaginal anterior colporrhaphy between June 1996 and May 1999 at a single institution (the Cleveland Clinic, Cleveland, OH). Subjects were randomized to one of three groups: standard anterior colporrhaphy without mesh (n=38), ultralateral anterior colporrhaphy without mesh (n=38), or anterior colporrhaphy with polyglactin 910 mesh (n=38). The investigators excluded patients if they were also scheduled to undergo an anti-incontinence procedure other than suburethral plication. Subjects also underwent correction of other prolapsed pelvic organs if present. Subjects underwent pelvic examinations for anatomic assessments and completed unspecified questionnaires about urinary symptoms and sexual function at baseline and at six months, one year, and two years post-operatively. The primary outcome variable in the initial analysis by Weber et al was anatomic success. For the reanalysis of the study data by Chmielewski et al, the primary outcome measure was success defined as no prolapse beyond the hymen, the absence of prolapse symptoms and the absence of retreatment.

The key results of the Weber/Chmielewski study were as follows:

- At a median follow-up of 23 months, there was no statistically significant difference between the three groups in anatomic results (10 of 33 subjects [30%] assigned to the standard colporrhaphy/non-mesh group experienced satisfactory

or optimal anatomic results, compared with 11 of 26 subjects [42%] in the mesh group and 11 of 24 subjects [46%] in the ultralateral colporrhaphy/non-mesh group, p=.578).
- There were no statistically or clinically significant differences between the groups in (a) the rate of prolapse beyond hymen, (b) the absence of pelvic organ prolapse symptoms, (c) reoperations for POP, and (d) all three outcomes combined.

The Weber/Chmielewski study had several limitations, including the following:

- The study was conducted at a single site, and the number of subjects was small.
- The mesh tested was absorbable, whereas most transvaginal POP repair surgeries involving mesh placement today involve a synthetic, non-absorbable mesh.
- There was significant variation in the type of procedures subjects underwent.
- Ten subjects (one in the standard colporrhaphy without mesh group, two in the ultralateral colporrhaphy group without mesh and seven in the mesh group) were lost to follow-up before one year post-operatively and were not included in the analysis.
- Seven subjects (two in the standard colporrhaphy without mesh group, four in the ultralateral colporrhaphy group without mesh and one in the mesh group) did not receive the allocated intervention and were excluded from the analysis.
- Subjects and investigators were not blinded to study group assignment.

Single-center, randomized, controlled trial of non-absorbable Parietene polypropylene mesh[14]

Sivaslioglu et al conducted a prospective, randomized, controlled trial in 90 women with cystocele who were undergoing transvaginal anterior colporrhaphy between January 2006 and January 2007 at a single institution (Ankara Etlik Women's and Maternity Teaching Hospital, Ankara, Turkey). The subjects were randomized to have surgery with (n=45) or without (n=45) placement of Parietene polypropylene mesh (Sofradim Production, Trévoux, France). The investigators excluded patients with stress urinary incontinence, rectocele, enterocele, or recurrent cystocele. All surgeries were performed by the same surgeon. Subjects were evaluated by pelvic examination for POP staging — performed by another surgeon who did not participate in the surgery — and a POP quality of life (P-QOL) questionnaire that had been validated for Turkish women.

The key results of the study were as follows:

- After a mean follow-up of 12 months (range eight to 16 months), an acceptable anatomic cure — defined as when the leading edge of the cystocele was less than minus one centimeter (cm) in relation to the hymen (stage 1 prolapse) — was achieved in 91% of mesh group subjects and 72% in non-mesh group subjects ($p<0.05$).

- Differences in anatomic cure rates were seen in anterior vaginal wall repairs, not in posterior wall repairs.
- Remarkable improvement in the scores of QOL was observed in both groups; post-operative P-QOL scores were reported as being the same for both groups.

The study had several limitations, including the following:

- The study was conducted at a single site and was relatively small.
- Two subjects in the mesh group and three subjects in the non-mesh group were lost to follow-up and were not included in the analysis.
- It was unclear whether subjects and all investigators were blinded to study group assignment.

Single-center, randomized, controlled trial of non-absorbable Perigree Transobturator Prolapse Repair System polypropylene mesh[15]

Nguyen et al conducted a prospective, randomized, controlled trial in 76 women with stage 2 or greater anterior vaginal prolapse who were undergoing transvaginal anterior colporrhaphy between January 2005 and April 2006 at a single institution (Kaiser Permanente Bellflower Medical Center, Bellflower, CA). The subjects were randomized to have surgery with (n=38) or without (n=38) placement of polypropylene mesh (Perigree Transobturator Prolapse Repair System, American Medical Systems, Minnetonka, MN) placed via a transobturator approach. The investigators excluded patients who had prior anterior vaginal prolapse repair with biologic or synthetic graft or were scheduled for concomitant Burch colposuspension or pubovaginal sling. Many subjects underwent other concomitant pelvic surgery. All surgeries were performed by the same surgeon. Prolapse staging and QOL evaluations (including the Pelvic Floor Distress Inventory [PFDI-20], Pelvic Floor Impact Questionnaire [PFIQ-7] and Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire [PISQ-12]) were performed at baseline and post-operatively at six months and one year. The primary outcome measure was recurrent stage 2 anterior vaginal prolapse. The subjects and the investigators performing the post-operative assessments were blinded to study group assignment.

The key results of the study were as follows:

- At one year, 87% of mesh group subjects and 55% of non-mesh group subjects had optimal and satisfactory anterior vaginal support (p=0.005). Most of the recurrences were POP-Q stage 2 and not bothersome enough to warrant reoperation.
- Sexual symptom scores as measured by the PISQ-12 did not change significantly in either study group following surgery.
- Total scores on the PFDI-20 and PRIQ-7 QOL questionnaires improved significantly from baseline in both groups at six months and one year post-operatively and were not statistically significantly different between the mesh and non-mesh groups at these time points.

The study had several limitations, including the following:

- The study was funded by American Medical Systems, Inc., the manufacturer of the mesh kit used in the study.
- The study was conducted at a single site and was relatively small.
- One subject in the mesh group did not undergo the assigned surgery and one subject in the non-mesh group was lost to follow-up. Both were excluded from the analysis.
- There was significant variation in the type of procedures subjects underwent.

Single-center, randomized, controlled trial of non-absorbable Gynemesh polypropylene mesh[16]

Carey et al conducted a prospective, randomized, controlled trial in 139 women with stage 2 or greater POP who required both anterior and posterior vaginal compartment repair at a single tertiary care teaching hospital (Royal Women's Hospital, Melbourne, Victoria, Australia). Subjects were randomized to transvaginal repair with (n=69) or without (n=70) placement of polypropylene mesh (Gynemesh PS, Ethicon, Inc.). The investigators excluded patients who required only an anterior or posterior vaginal compartment repair, had prolapse of the vaginal vault or cervix beyond the hymen, or required abdominal prolapse surgery with mesh. The primary outcome measure was absence of POP stage 2 or greater at 12 months. Secondary outcomes were symptoms, QOL outcomes (as assessed by the Prolapse Symptom Inventory & QOL questionnaire), and satisfaction with the surgery.

The key results of the study were as follows:

- Assuming that all subjects lost to follow-up prior to the 12-month post-operative evaluation were failures, the objective success rate (absence of POP stage 2 or greater) at 12 months was significantly greater in the mesh group subjects (81% versus 66% in the non-mesh group, p=0.049).
- Excluding patients who were lost to follow-up, there was no statistically significant difference in the primary outcome measure (81% of subjects in the mesh group had no stage 2 or greater POP at 12 months versus 66% in the no-mesh group, p=0.07). Carey et al highlighted this result in their report and concluded that vaginal surgery augmented by mesh did not result in significantly less recurrent prolapse at 12 months following surgery than traditional colporrhaphy without mesh.
- Most recurrences of stage 2 POP were in the anterior compartment
- A high level of satisfaction with surgery and improvements in symptoms and QOL measures at 12 months compared to baseline were observed in both groups, and there were no statistically significant differences in symptoms, QOL measures, or satisfaction with surgery between the two groups.
- Awareness of prolapse at 12 months was seen in three subjects (4.9%) in the mesh group versus seven (11.3%) in the non-mesh group (p=0.32).

- There was no difference in de novo dyspareunia (pain with intercourse) post-operatively.

The study had several limitations, including the following:

- The study was funded by Ethicon, Inc., the manufacturer of the mesh kit used in the study.
- The study was conducted at a single site.
- Subjects and investigators were not blinded to study group assignment.
- Six subjects in the mesh group and nine subjects in the non-mesh group were lost to follow-up before the 12-month follow-up assessment. All subjects were included in the intention-to-treat analysis presented here.
- There was variation in the type of procedures individual subjects underwent.

Multicenter, randomized, controlled trial of non-absorbable Prolift polypropylene mesh[17]

Iglesia et al conducted a prospective, randomized, controlled, double-blind trial in 65 women with uterovaginal or vaginal prolapse, stages 2 to 4, who were undergoing transvaginal reconstructive surgery between January 2007 and August 2009 at three academic medical centers (Washington Hospital Center, Washington, DC; Stanford University, Stanford, CA; and Yale University, New Haven, CT). Subjects were randomized to traditional transvaginal prolapse surgery with (n=32) or without (n=33) placement of synthetic monofilament polypropylene mesh (Prolift mesh, Ethicon, Inc.) using a transobturator and ischiorectal fossa approach. The investigators excluded patients with shortened vagina or other congenital pelvic anomalies, other laparoscopic or abdominal/pelvic surgery in the previous three months, known neurologic or medical conditions affecting bladder function, or the need for concurrent surgery requiring an abdominal incision. The primary outcome measure was objective treatment success (POP-Q stage 1 or less) at three months. Secondary outcome measures included QOL measures (PFDI-20, PFIQ-7, PISQ-12, Pelvic Organ Prolapse Distress Inventory, Colorectal Anal Distress Inventory, Urogenital Distress Inventory [UDI-6], Colorectal Anal Impact Questionnaire, Urinary Impact Questionnaire, Patient Global Impression of Improvement [PGI-I], and Patient Global Impression of Severity) and complication rates. Subjects and investigators conducting post-operative evaluations were blinded to study group assignment unless it was medically necessary to break the blind.

The key results of the study were as follows:

- The study was halted, following an interim analysis by a data safety and monitoring board (DSMB), due to predetermined stopping criteria for vaginal mesh erosion (sometimes referred to as “mesh exposure”) at a median of 9.7 months. All subjects had been followed for at least three months.
- There was no statistically significant difference in overall recurrence of POP-Q stage 2 or greater between the study groups (59% in the mesh group versus 73% in the non-mesh group, p=0.28).
- Most recurrences of POP (77%) were at or proximal to the hymenal remnant.

- There was no statistically significant difference in anterior or posterior wall recurrence.
- Subjective cure of bulge symptoms was noted in 94% of mesh subjects and 100% of non-mesh subjects
- There were no differences between the mesh and non-mesh groups in the multiple subjective QOL measures at three months post-operatively.
- Five subjects (15.6%) in the mesh group developed vaginal erosions. Erosions occurred at two weeks (one subject), six weeks (two subjects), seven weeks (one subject), and two months (one subject). Three subjects underwent surgery to remove the mesh.

The limitations of the study included:

- The study was small and had only short-term follow-up.
- There was variation in the type of procedures individual subjects underwent.

Multicenter, randomized, controlled trial of non-absorbable Parietene polypropylene mesh[7]

Nieminen et al conducted a prospective, randomized, controlled trial in 202 women with symptomatic anterior vaginal wall prolapse to the hymen or beyond who were undergoing transvaginal prolapse repair between April 2003 and May 2005 at five hospitals (Tampere University Hospital, Tampere, Finland; Central Hospital of South Ostrobothnia, Seinäjoki, Finland; Central Hospital of Kanta-Häme, Hämeenlinna, Finland; Central Hospital of Päijät-Häme, Lahti, Finland; and Central Hospital of Central Finland, Jyväskylä, Finland). Subjects were randomized to transvaginal colporrhaphy with (n=105) or without (n=97) placement of tailored polypropylene mesh (Parietene light, Sofradim Production). The investigators excluded patients requiring concomitant vaginal vault suspension such as sacrospinous ligament fixation or sacral colpopexy for vaginal prolapse or uterine procidentia, surgery for stress urinary incontinence, or laparotomy or laparoscopy for any reason. Subjects could undergo other transvaginal prolapse repairs. Outcomes were assessed by pelvic examination and standard symptom questionnaires at two, 12, 24, and 36 months post-operatively. The primary outcome measure was anatomic recurrence of anterior vaginal prolapse at POP-Q stage 2 or greater within three years after repair. Secondary outcomes were symptom resolution, reoperation rate, and mesh exposure.

The key results of the study were as follows:

- Recurrence of anterior vaginal wall prolapse occurred in 41% of subjects in the non-mesh group and 13% of subjects in the mesh group ($p<0.0001$).
- There were no statistically significant differences between groups in recurrent apical or posterior prolapse.
- The majority of the prolapse recurrences greater than POP-Q stage 1for both groups combined were at POP-Q stage 2 (94%).

- There were no statistically significant differences between groups in symptom measures, including dyspareunia.

The study had several limitations, including the following:

- Neither the subjects nor the investigators were blinded to study group assignment.
- The QOL questionnaires were not validated.
- There was variation in the type of procedures individual subjects underwent.

Multicenter, randomized, controlled trial of non-absorbable Prolift polypropylene mesh[18]

Withagen et al conducted a prospective, randomized, controlled trial in 194 women with recurrent POP, stage 2 or higher, involving the anterior vaginal wall, posterior vaginal wall, or both, who were undergoing transvaginal colporrhaphy between June 2006 and July 2008 at 13 medical centers in the Netherlands. Subjects were randomized to have transvaginal surgery with (n=95) or without (n=99) placement of polypropylene mesh (Prolift, Ethicon, Inc.) implantation (two subjects in each group did not undergo surgery following randomization). The investigators excluded patients who had prior prolapse surgery with mesh. Outcomes were assessed by pelvic examination at six weeks and at six and 12 months and by standard symptom questionnaires (UDI-6, PGI-I, Defecatory Distress Inventory [DDI], and Incontinence Impact Questionnaire) at six and 12 months. The primary outcome measure was anatomic failure in the treated vaginal compartment (POP stage 2 or higher). Secondary outcomes included subjective improvement, effects on bother and QOL, duration of surgery, blood loss, length of hospitalization and adverse events.

The key results of the study were as follows:

- The failure rate at 12 months was 45% in the non-mesh group subjects and 10% in the mesh group subjects ($p<0.001$).
- Anatomic results were better in the mesh group subjects for both anterior and posterior wall POP.
- Most of the anatomic failures were stage 2 and not bothersome enough to lead to re-intervention.
- Except for statistically significant slightly higher scores for pain and incontinence on the DDI questionnaire in the non-mesh group, symptoms and QOL measures were not statistically significantly different at 12 months between the study groups.
- Subjective improvement was reported by 64 of 80 subjects (80%) in the non-mesh group and 63 of 78 subjects (81%) in the mesh group.
- There was no statistically significant difference in perceived prolapse between groups.
- There were no statistically significant differences in dyspareunia or post-operative stress urinary incontinence between groups.

The study had several limitations, including the following:

- The authors have ties to Ethicon, Inc., the manufacturer of the mesh kit used in the study.
- The subjects and investigators were not blinded to study group assignment.
- Surgery was not performed in two subjects randomized to each group, and three subjects in the mesh group and one subject in the non-mesh group were lost to follow-up.
- There was variation in the type of procedures individual subjects underwent.

Multicenter, randomized, controlled trial of non-absorbable Gynecare Prolift Anterior Pelvic Floor Repair System polypropylene mesh[19]

In one of the most recent and best designed studies, Altman et al conducted a prospective, parallel-group, randomized, controlled trial in 389 women with stage 2 or higher prolapse of the anterior vaginal wall (cystocele) and symptoms of vaginal bulging or pelvic heaviness who were undergoing transvaginal anterior colporrhaphy between December 2007 and December 2008 at 53 hospitals throughout Sweden, Norway, Finland, and Denmark. The subjects were randomized to have the surgery with (n=200) or without (n=189) transvaginal placement of polypropylene mesh (Gynecare Prolift Anterior Pelvic Floor Repair System kit, Ethicon, Inc.). The investigators excluded patients needing concomitant surgery. The study was monitored by a DSMB. Subjects underwent pelvic examinations and completed questionnaires (UDI-6 and PISQ-12) about symptoms related to pelvic organ prolapse, urinary incontinence, and sexual function at two and 12 months post-operatively. The primary outcome measure was a composite of objective and subjective measures: POP stage 0 (no prolapse) or 1 (position of anterior vaginal wall more than 1 cm above the hymen) and a negative response to the question, “Do you experience a feeling of bulging or protrusion in the vaginal area?” The manufacturer of the mesh kits did not provide the kits for the study and had no involvement in its conduct, but did partially fund the study through a grant.

The key results of the study were as follows:

- Baseline characteristics were similar for both groups.
- At one year, the primary outcome (no prolapse on the basis of objective and subjective criteria) was seen in 60.8% in mesh group and 34.5% in the non-mesh group ($p<0.001$).
- At one year, 82.3% of subjects in the mesh group had stage 0 or 1 POP versus 47.5% of subjects in the non-mesh group ($p<0.001$).
- At one year, 75.4% of subjects in the mesh group had no symptoms of vaginal bulging versus 62.1% of subjects in the non-mesh group ($p=0.008$)
- Mean Urogenital Distress Inventory questionnaire scores at one year were the same for both groups.
- Mean Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) scores at one year were the same for both groups.

The study had the following limitations:

- The study was partially funded by Ethicon, Inc., the manufacturer of the mesh kit used in the study.
- The primary analyses were not intention-to-treat.
- Investigators performing the follow-up anatomic evaluations were not blinded to study group assignment.

Systematic reviews and meta-analyses

In 2008, Jia et al published a systematic review and meta-analysis on the efficacy and safety of using mesh or grafts in surgery for anterior or posterior vaginal wall prolapse.[6] Their study, funded by the United Kingdom's National Institute for Health and Clinical Excellence, included a review of 49 studies, of which only six were full-text randomized, controlled trials. Of the six full-text randomized, controlled trials, only two involved placement of mesh, and polyglactin 910 mesh was used in both.[11,12,13] Therefore, the applicability of the efficacy findings of this review and meta-analysis to the current practice of using synthetic polypropylene mesh for POP repairs is very limited. Key findings and conclusions from the Jia et al review were as follows:

- There is some evidence that mesh or biologic grafts were better than no mesh or grafts for preventing objectively determined recurrence of anterior prolapse. Non-absorbable synthetic mesh had a statistically significant lower objective failure rate than absorbable synthetic mesh (OR 0.23, 95% CI 0.12 to 0.44).
- There were too few data to draw conclusions about posterior prolapse repairs.
- Evidence for most outcomes was too sparse to provide meaningful conclusions. Rigorous long-term randomized controlled trials are required to determine the comparative efficacy of using mesh or grafts.

In 2010, Maher et al published a Cochrane Database systematic review on the surgical management of POP in women.[4] The review covered a wide range of surgical procedures for treating POP, including comparisons of POP repairs with and without various types of surgical mesh and biological grafts. Key findings and conclusions from the Maher et al review regarding the placement of surgical mesh during transvaginal POP repair were as follows:

- For anterior vaginal wall prolapse, standard anterior repair without mesh placement was associated with more recurrent cystoceles than repair with placement of polyglactin mesh (RR 1.39, 95% CI 1.02 to 1.90), but data on morbidity or other clinical outcomes is lacking.
- For anterior vaginal wall prolapse, standard anterior repair without mesh placement was associated with more anterior compartment failures on examination than repair with placement of polypropylene mesh (RR 2.14, 95% CI 1.23 to 3.74) or armed transobturator mesh (RR 3.55, 95% CI 2.29 to 5.51). Of

note, Maher et al warned that data relating to polypropylene mesh was extracted from conference abstracts without any peer-reviewed manuscripts being available and should be interpreted with caution.

- No data exist on the efficacy of placement of polypropylene mesh in the posterior vaginal compartment.
- There were no differences between POP repairs with or without mesh placement in terms of subjective outcomes, QOL data, de novo dyspareunia, de novo stress urinary incontinence, or re-operation rates for prolapse or stress urinary incontinence.

Summary conclusions regarding benefits of placing synthetic surgical mesh during transvaginal repair of POP

In their 2008 systematic review, Jia et al made the following important observation regarding the assessment of the efficacy of POP repair procedures:[6]

> The conundrum in prolapse surgery is that objective prolapse recurrence is not necessarily related to continuation of prolapse symptoms (subjective failure). It is increasingly [recognized] that in prolapse surgery, **subjective failure is a more appropriate outcome measure of efficacy than objective failure**… In the present review, only a few studies reported data on subjective prolapse symptoms and other genitourinary symptoms of importance to women (urinary, bowel and sexual function). [emphasis added]

Furthermore, in the recently published re-analysis of their 2001 study,[12] Chmielewski et al noted that the definition for defining a successful outcome for POP repair surgery has evolved over the past decade:[13]

> The definition of *success* that was used in [the original publication of their] trial was based on recommendations of the 2001 National Institutes of Health (NIH) Workshop on Standardization of Terminology for Researchers in Pelvic Floor Disorders. The workshop noted that these definitions were made arbitrarily and without the benefit of adequate knowledge of the epidemiology and natural history of POP or the relationship between anatomic support and pelvic floor symptoms. Since this workshop, advances in research have revealed these purely anatomic definitions to be too strict, because >75% of women who had annual gynecologic examinations without symptoms of POP would not meet the definition of “optimal anatomic outcome” and almost 40% of the women would not meet the definition of “satisfactory anatomic outcome.” Thus, studies that use even the NIH “satisfactory” anatomic outcome as their definition of treatment success…classify a substantial number of women within the spectrum of normal anatomy as treatment failure.

Keeping these important observations in mind, the following is a summary of the efficacy data from the research presented above:

- Although most randomized, controlled clinical trials evaluating the use of surgical mesh in transvaginal POP repair have many limitations, the available data from the peer-reviewed scientific literature reveal that, while transvaginal POP repair with mesh often results in less prolapse being detected on pelvic examination following surgery when used for anterior vaginal wall repairs in comparison to non-mesh repairs using only native tissues, there is little evidence that POP repair surgery with mesh results in any better outcomes in terms of relief of symptoms and QOL measures, which ultimately are the clinically significant indicators for measuring treatment success for this condition.
- There is no evidence that transvaginal apical or posterior wall repair with mesh results in a better anatomic outcome than repair without mesh.
- Most of the recurrences of prolapse following transvaginal surgery, with or without mesh placement, are at a low stage, are asymptomatic, and do not require further intervention.
- To date, no study comparing transvaginal surgery for anterior wall prolapse with surgical mesh placement to surgery without mesh has demonstrated a clinically significant difference in terms of subjective success, QOL outcomes, and reoperation for prolapse or incontinence.

The FDA reached similar conclusions in its analysis.[3]

B. Safety assessment: the use of surgical mesh for transvaginal POP repair commonly causes serious complications

While a review of the peer-reviewed scientific literature reveals little evidence that placement of surgical mesh during transvaginal POP repair offers any clinically significant benefits, it does demonstrate that use of mesh leads to a high rate of serious complications, many of which require additional surgical intervention and some of which are not amenable to surgical correction and result in permanent life-altering harm to women.

Randomized, controlled clinical trials

The randomized, controlled clinical trials, particularly small trials such as those discussed above for transvaginal POP repair, typically fail to identify important safety signals. However, the prospective, randomized, controlled trials testing synthetic mesh placement in women with POP identified several serious safety problems:

- Mesh erosions, a problem obviously limited to subjects assigned to the surgical mesh groups, was reported in all trials testing synthetic non-absorbable polypropylene mesh. The percent of subjects who had this adverse event across all studies ranged from 5% to 19% (13% for all mesh group subjects for all studies combined).[7,14-18] Many of these subjects needed additional surgery to correct the mesh erosion.[7,14-19] Mesh erosions were seen as early as two weeks after surgery.[17]

- Less commonly reported adverse events that occurred more frequently in mesh subjects than in non-mesh subjects participating in some of the randomized clinical trials included de novo urinary incontinence, bladder perforations, and pelvic hematomas.
- In the largest randomized, controlled trial conducted to date, Altman et al noted the following regarding the duration of surgery, intraoperative blood loss, and post-operative complications in subjects undergoing transvaginal POP repair with (n=200) or without (n=189) placement of surgical mesh:[19]
    - Surgery lasted longer (52.6 versus 33.5 minutes) and intraoperative blood loss was higher (84.7 versus 35.4 milliliters [mL]) in the mesh group, ($p<0.0001$ for both).
    - Rates of bladder perforation were 3.5% in the mesh group and 0.5% in the non-mesh group ($p=0.07$).
    - Rates of new stress urinary incontinence after surgery were 12.3% in the mesh group and 6.3% in the non-mesh group ($p=0.05$).
    - Pain during sexual intercourse was reported as “usually” or “always” by 2% of subjects in the non-mesh group and 7.3% in the mesh group ($p=0.07$).

With regards to the development of de novo stress urinary incontinence, Ek et al conducted a multicenter, randomized sub-study at five sites participating in the larger randomized study by Altman et al.[20] As part of the substudy, subjects with symptomatic stage 2 or higher anterior POP — who were randomized to anterior transvaginal mesh surgery or traditional colporrhaphy without mesh in the parent study — underwent multichannel urodynamic testing, including cough test prior to anterior vaginal wall prolapse surgery and two months after surgery, to assess for the development and pathophysiology of de novo stress urinary incontinence following POP repair. A total of 50 subjects participated in the sub-study, with 23 randomized to the mesh group and 27 randomized to the non-mesh group. One subject in each group was lost to follow-up before the two-month post-operative re-testing, so 22 mesh group subjects and 26 non-mesh group subjects were studied at two months post-surgery.

The key results of the study were as follows:

- In the non-mesh group, there were no significant differences in any of the urodynamic variables when comparing pre- and post-operative measures.
- In the mesh group, the number of subjects with a maximal urethral closing pressure (MUCP) at a level lower than 40 cm of H_2O on urodynamic testing increased following POP repair surgery, although this was not statistically significant from baseline testing ($p=0.18$). However, the number of subjects in the mesh group with objective leakage during the post-operative cough provocation increased significantly in comparison to baseline testing ($p=0.016$).
- There was a significantly greater number of subjects with de novo leakage at cough provocation after mesh surgery compared to non-mesh surgery (7 of 22 [32%] versus 2 of 25 [8%], $p=0.038$).

The investigators concluded that transvaginal POP surgery for anterior vaginal wall prolapse with mesh results in a lowering of MUCPs, increasing the risk for de novo stress urinary incontinence, compared to standard anterior colporrhaphy without mesh.

Systematic reviews and meta-analyses

Several systematic reviews of the peer-reviewed scientific literature demonstrated that the mesh erosion rate with transvaginal POP repair ranged from 10% to 14% for non-absorbable polypropylene mesh.[4,6,21,22] Additional surgery frequently was needed to treat these mesh erosions. Some patients need multiple surgeries to treat the erosions.[21]

Additional post-operative complications seen more commonly following transvaginal POP repair with synthetic mesh placement in comparison to surgery without mesh include wound granulation (6.8% of patients)[21] and urogenital fistulae (0.2%),[23] which usually require surgical correction.

Prospective observational studies and retrospective case series

Milani et al conducted a prospective observational study of 63 women undergoing anterior or posterior transvaginal surgery for POP with non-absorbable polypropylene mesh (Ethicon, Inc.) at two tertiary hospitals in Italy with follow-up up to one year.[24] They reported that 13% of patients had mesh erosion following anterior vaginal wall repair and 6.5% had mesh erosion following posterior wall repair. Also, the prevalence of dyspareunia increased by 20% and 63% in patients undergoing anterior and posterior vaginal wall repairs, respectively, in comparison to baseline symptoms. The investigators concluded that while good anatomic results were achieved with polypropylene mesh procedures for prolapse repair, there was a high rate of morbidity. They stated, “We believe that the use of [polypropylene] mesh should be abandoned.”

Miller et al conducted a prospective case series study of 85 women with symptomatic POP (POP-Q stage 2 to 4) who underwent transvaginal prolapse repair surgery with Gynemesh PS Prolene Nonabsorbable Soft Mesh (Ethicon, Inc.) between January and December 2004 at three medical centers in the U.S.[25] The patients were followed for five years. They reported the following complications:

- Mesh exposure was seen in 16 of 85 patients (19%); 6 patients had recurrent episodes of mesh exposure.
- Eight patients required partial mesh excision.
- Three patients experienced some degree of dyspareunia.
- One patient developed a rectovaginal fistula.
- Two patients had ureteral injuries, one of which resulted in a ureterovaginal fistula.

Fatton et al performed a retrospective case review of 110 consecutive patients undergoing transvaginal repair of POP with placement of synthetic non-absorbable polypropylene mesh (Gynecare Prolift, Ethicon, Inc.) between February and September 2005 at three hospitals in France.[26] The patients were followed for up to six months post-operatively. The investigators identified the following post-operative complication rates:

- Five patients (4.7%) had mesh exposure, two of whom required surgical management.
- Seventeen percent of patients had mesh shrinkage.
- Granuloma without mesh exposure was seen in 2.8% of patients.
- De novo urination disorders were seen in 9.7% of patients.
- Nine percent of patients without stress urinary incontinence before POP repair developed de novo stress urinary incontinence post-surgery.

Caquant et al conducted a much larger retrospective medical record review of 684 patients who underwent surgical repair of POP at stage 3 or greater via the vaginal route with interposition of non-absorbable synthetic mesh (Gynemesh Prolene Soft, Ethicon, Inc.) between October 2002 and December 2004 at seven medical centers in France.[27] The patients were followed for six months post-operatively. The review identified the following complication rates:

- Peri-surgical complications occurred in 2% of patients:
  - Five bladder wounds (0.7%)
  - One rectal wound (0.15%)
  - Seven hemorrhages greater than 200 mL (1%)
- During the first month post-operatively, complications occurred in 2.8% of patients:
  - Two pelvic abscesses (0.29%)
  - 13 pelvic hematomas (1.9%)
  - One pelvic cellulitis (0.15%)
  - Two vesicovaginal fistulae (0.29%)
  - One rectovaginal fistula (0.15%)
- Late post-operative complications occurred in 33.6% of patients:
  - 77 mesh exposures (11.3%), 46 of which required surgical intervention
  - 80 mesh retractions (11.7%), of which 19 required surgery and 52.6% were associated with mesh exposure
  - 37 cases of de novo stress urinary incontinence (5.4%)

Aungst et al performed a retrospective medical record review of 335 consecutive cases of women with stage 2 or higher vaginal prolapse who underwent surgery with non-absorbable polypropylene mesh (Prolift, Ethicon, Inc.) between July 7, 2005 and January 31, 2008 at three medical centers in the U.S.[28] Seventy-three percent underwent combined anterior and posterior vaginal wall repair, 20% underwent anterior

vaginal wall repair only, and 7% posterior vaginal wall only. The investigators reported the following complications.

- Ureter injury occurred in one patient during passing of deep anterior Prolift guide.
- The intraoperative visceral injury rate was 6.6% (18 bladder perforations, three ureteral injuries, and one rectal injury)
- Mesh exposure occurred in 3.8% of patients.
- Post-operative de novo stress urinary incontinence was seen in 24.3% of patients.
- Eighteen percent of patients had pelvic muscle symptoms (new-onset dyspareunia, vaginal pain, groin pain, pain while walking, and pain with sitting), 74% of which resolved within six months.

The investigators concluded that pelvic muscle dysfunction and de novo stress urinary incontinence will be encountered post-operatively in a moderate number of women undergoing POP repair with mesh.

Finally, Feiner and Maher described an uncommon, but particularly serious complication caused by the use of surgical mesh in transvaginal POP repair that severely impacted the QOL of the patients.[29] They reported a retrospective case series of 17 consecutive women who underwent surgical intervention between January 2007 and December 2008 at a tertiary care hospital in Australia for vaginal mesh contraction after prolapse repair with non-absorbable polypropylene mesh kits. In all cases, the type of mesh kit used for prolapse repair was either anterior mesh alone or combined anterior and posterior mesh kits. The patients' presenting symptoms included the following:

- Severe vaginal pain, aggravated by movement (17 of 17)
- Dyspareunia in all sexually active patients (14 of 14)
- Focal tenderness over contracted portions of mesh on vaginal examination (17 of 17)
- Mesh erosion (9 of17)
- Vaginal tightness (7 of 17)
- Vaginal shortening (5 of 17)

The patients underwent subsequent surgical intervention with mobilization of mesh from underlying tissue, division of fixation arms of the central graft, and excision of contracted mesh. The outcomes of the corrective surgical interventions were as follows:

- A substantial reduction in vaginal pain was experienced by 88% (15 of 17).
- A substantial reduction in dyspareunia was experienced by 64% (9 of 11).
- Three patients required subsequent excision of the entire accessible mesh because of persistent symptoms.

Feiner and Maher concluded that vaginal mesh contraction is a serious complication after prolapse repair with armed polypropylene mesh and is associated with substantial morbidity, frequently requiring surgical intervention.

The FDA's review of data from the agency's Manufacturer and User Facility Device Experience (MAUDE) database

On October 20, 2008, the FDA issued a public health safety notification regarding serious complications associated with transvaginal placement of surgical mesh to treat POP or stress urinary incontinence.[30] Most surgical mesh devices cleared by the FDA for transvaginal surgical POP repair are composed of non-absorbable synthetic polypropylene.[3] The FDA reported that over the preceding three years, the agency had received over 1,000 reports from nine surgical mesh manufacturers of complications that were associated with surgical mesh devices used to repair POP and stress urinary incontinence. The most frequent complications reported to the FDA at that time included erosion through vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and incontinence. There were also reports of bowel, bladder, and blood vessel perforation during insertion of the mesh. In some cases, vaginal scarring and mesh erosion led to a significant decrease in patient QOL due to discomfort and pain, including dyspareunia.

On July 13, 2011, the FDA issued an updated safety communication on serious complications associated with transvaginal placement of surgical mesh to treat POP.[31] The agency reported that serious complications associated with surgical mesh for transvaginal repair of POP "are **not rare**" [emphasis in the original]. The FDA further stated:

> This is a change from what the FDA previously reported on Oct. 20, 2008. Furthermore, it is not clear that transvaginal POP repair with mesh is more effective than traditional non-mesh repair in all patients with POP and it may expose patients to greater risk.

In a report that accompanied the FDA's July 13, 2011 safety communication, the agency reported the following data based upon the agency's search of the MAUDE database:[3]

> The FDA conducted a search of the…MAUDE…database for medical device reports (MDRs) of adverse events associated with all urogynecologic surgical mesh products received from January 1, 2005 - December 31, 2010. The search identified 3,979 reports of injury, death, and malfunction. Among the 3,979 reports, 2,874 reports were received in the last 3 years (January 1, 2008 - December 31, 2010), and included 1,503 reports associated with POP repairs and 1,371 associated with [stress urinary incontinence] repairs. The number of MDRs associated with POP repairs increased by more than 5-fold compared to the number of reports received in the previous 3 years (January 1, 2005 - December 31, 2007).

> Multiple factors can affect MDR reporting, including increased use of urogynecologic surgical mesh in the clinical community, increased awareness on the potential adverse events associated with mesh after the 2008 *PHN*, an increased number of new POP meshes on the market, or an increase in the number of actual adverse events associated with mesh. Determining the exact cause or causes of the increase is difficult. **Regardless, the FDA believes the overall increase in the number of serious adverse event reports is cause for concern.** [emphasis added]
>
> From 2008 to 2010, the most frequent complications reported to the FDA from the use of surgical mesh devices for POP repair included vaginal mesh erosion (also called exposure, extrusion or protrusion), pain (including painful sexual intercourse known as dyspareunia), infection, urinary problems, bleeding, and organ perforation. There were also reports of recurrent prolapse, neuro-muscular problems, vaginal scarring/shrinkage and emotional problems. Many of the MDRs cited the need for additional intervention, including medical or surgical treatment and hospitalization. Vaginal shrinkage was not reported in the previous three year period corresponding to the 2008 [Public Health Notification].
>
> Between 2008 and 2010, there were seven reported deaths associated with POP repairs. Follow-up investigation on the death reports revealed that three of the deaths associated with POP repair were related to the mesh placement procedure (two bowel perforations, one hemorrhage). Four deaths were due to post-operative medical complications not directly related to the mesh placement procedure.

Summary and conclusions regarding the safety of placing synthetic surgical mesh during transvaginal repair of POP

Based on the above review of the peer-reviewed scientific literature and the FDA's analysis of reports submitted to the MAUDE database, the following conclusions can be drawn:

- Synthetic surgical mesh placed during transvaginal repair of POP commonly causes many serious adverse events.
- Patients who undergo transvaginal POP repair with surgical mesh are subject to many mesh-related complications that do not occur in patients who undergo POP repair without mesh.
- The most common complication caused by surgical mesh used in transvaginal POP repair is mesh erosion. This adverse event occurs in approximately 10% of women undergoing transvaginal POP repair with surgical mesh.
- More than half of the women who develop mesh erosions from non-absorbable, synthetic mesh require surgical excision. Some women require two or more additional surgeries.
- Some adverse events, such as mesh contraction, can be life-altering for some women. Sequelae (e.g., pain) may continue despite mesh removal.

- New-onset stress urinary incontinence has been reported to occur more frequently following transvaginal POP repair with mesh than repair without mesh.

Again, the FDA reached similar conclusions in its analysis.[3]

C. Overall risk:benefit assessment for transvaginal repair of POP with placement of non-absorbable surgical mesh

In order for a medical treatment to be ethically justified, the overall benefits of the intervention must outweigh the risks. For the currently available non-absorbable surgical mesh products specifically designed and labeled for transvaginal repair of POP, there is little evidence from the published prospective, randomized, controlled clinical trials that using such mesh provides clinically significant benefits in comparison to POP repair procedures without mesh. In fact, the available data indicate that in terms of subjective symptoms and QOL measures — which are the critical measures for assessing the efficacy of treatment for a condition that is not life-threatening — there is no clinically significant difference between transvaginal POP repair with and without placement of surgical mesh.

On the other hand, the use of non-absorbable synthetic surgical mesh during transvaginal repair of POP causes many common, serious adverse events that are not seen with non-mesh procedures.

Given the absence of evidence for clinically significant benefit and the overwhelming evidence of very serious, common risks, use of synthetic surgical mesh products for transvaginal repair of POP is not ethically justifiable.

D. Failure of the 510(k) premarket notification process to protect the health and welfare of women undergoing POP repair with surgical mesh

The data summarized in this petition provides a “poster-child” example of the fundamental failure of the 510(k) premarket notification process to protect the public’s health and welfare. Multiple mesh devices specifically designed for transvaginal POP repair were allowed by the FDA to come onto the U.S. market, based only on in vitro and animal testing data and a determination of substantial equivalence to other surgical mesh products already on the market. Despite a complete lack of clinical data demonstrating that these mesh devices were reasonably safe and effective for transvaginal repair of POP, these devices have been heavily promoted by industry and their highly paid physician consultants. As a result, tens of thousands of women have been seriously harmed, many permanently.

E. Commercial interests related to surgical mesh kits for POP repair have taken precedence over patient safety and welfare

In a commentary criticizing the commercial pressures that have led to the proliferation in the use of commercial surgical mesh kits for POP repair, as well as to recent revisions

to the American College of Obstetricians and Gynecologists (ACOG) Practice Bulletins on POP that resulted in a downplaying of the experimental nature of these commercial products, Wall (a co-petitioner on this petition) and Brown noted the following:[32]

> "[Trocar]-and-mesh" device kits for the surgical correction of prolapsed female genitalia are now the rage. New variations on this theme arrive in the medical marketplace with stunning frequency. There is now virtually no cavity in the pelvis that cannot have an artificial mesh threaded through it with the use of a strong right arm and a long enough spike. Whether or not this surgical intervention is good for patients and not just good for surgeons' pocketbooks and the balance sheets of surgical device manufacturers is as yet unknown because appropriately powered clinical trials with adequate follow-up have not yet been performed, but it is clear that powerful commercial interests are attempting to reshape the field of pelvic surgery for their financial benefit. Operations tied to specific commercial products are being carried out and promoted by groups who stand to benefit directly from their utilization, irrespective of whether or not the operation in question is in the patient's best interests. This sad reality raises significant ethical questions for pelvic surgeons, for professional associations such as [ACOG], and for governmental regulators. We contend that these issues are not being adequately addressed…
>
> There are clear differences between what is legal and what is ethical with regard to the use of surgical devices such as the ever-expanding number of [trocar]-and-mesh kits now marketed for the treatment of incontinence and prolapse. Unlike drugs—which must be shown by clinical trials to be both safe and effective prior to their release—current regulations in the USA do not require medical devices such as the mesh kits for incontinence surgery and prolapse repair to meet this burden of proof [1]. If the Food and Drug Administration decides that a device is "equivalent" to something that has already been cleared for release, it is allowed to enter the market. Independent clinical trials are not currently required. Thus, permission to allow a new device to enter the market is largely a *political* decision; but *legal* permission to market a device is not the same as using it in an *ethical* manner…
>
> [ACOG] should throw its considerable weight behind efforts to bring the legal requirements for marketing new devices in line with our profession's ethical obligations to our patients. New medical or surgical devices should not be allowed into the American or any other world market until there is definitive evidence of the devices' safety and efficacy on the basis of properly designed, properly powered clinical trials. Rather than changing policy to accommodate enhanced reimbursement for ethically questionable practices, ACOG should push for more stringent regulatory control of the medical device industry.

In a subsequent letter to the editor responding to the Wall and Brown commentary, Weber reported the following:[33]

> As the author responsible for the controversial [use of the word "experimental" in the prior version of] the ACOG Practice Bulletin on pelvic organ prolapse, I would like to thank Drs. Wall and Brown for bringing this matter to the attention of clinicians, and Dr. Karram and the *International Urogynecological Journal* for their willingness to publish this.
>
> The explanation I was given at the time why ACOG decided to change the wording (over my strenuous objections) was that the meaning of the word "experimental" was ambiguous. This is disingenuous at best. In fact, the ACOG staff member at the meeting of the Committee on Practice Bulletins — Gynecology described the real reason for concern: "…recognition that the current wording would possibly deny payment for some physicians." Most of the clinicians who objected to the word "experimental" understood only too well exactly what meaning was intended — that the use of mesh kits as procedures for prolapse lacked sufficient evidence of risk versus benefit to adequately counsel patients as to expected outcomes. Such clinicians were concerned that insurance companies would not cover procedures labeled experimental, and they were concerned about their medicolegal risk should a complication arise in the course of procedures labeled experimental. Exactly the kinds of concerns that a professional organization that truly promoted best medical practices would see as a red flag — that clinicians' concerns were not focused on what was best for the patient, but on what protected their income. That ACOG chose to align itself with these few Fellows at the expense of patients' outcome and safety is of grave concern.

III. SUMMARY OF REQUESTED ACTIONS

In summary, given (a) the absence of evidence for clinically significant benefits for all currently available non-absorbable surgical mesh products specifically designed and labeled for transvaginal repair of POP; and (b) the overwhelming evidence of very serious adverse events commonly caused by these devices, Public Citizen hereby petitions the FDA, pursuant to the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 360f and 360h, and 21 C.F.R. §§ 10.30, 810, and 895, to immediately:

(1) ban the marketing of all currently available non-absorbable surgical mesh products specifically designed and labeled for transvaginal repair of POP because these devices present "an unreasonable and substantial risk of illness or injury," the standard for the FDA to institute proceedings to ban a device under the device law, 21 U.S.C. § 360f and 21 C.F.R. § 895.21(a);

(2) order all manufacturers of non-absorbable surgical mesh products specifically designed and labeled for transvaginal repair of POP to recall these products; and

(3) require that any non-absorbable surgical mesh product specifically designed and labeled for transvaginal repair of POP that is proposed for marketing in the future

be classified as a class III device and only be approved for marketing under a PMA that includes data from well-designed, prospective clinical trials that provide a reasonable assurance that the surgical mesh product is safe and effective.

IV. ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this petition will have an impact on the environment.

V. CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

Michael A. Carome, M.D.
Deputy Director
Public Citizen's Health Research Group

Sidney M. Wolfe, M.D.
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[1] Title 21 Code of Federal Regulations, Part 878, Subpart D (prosthetic devices), section 878.3300. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=878.3300. Accessed August 3, 2011.
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