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Selection of patients in whom vaginal graft use may be appropriate

Consensus of the 2nd IUGA Grafts Roundtable: Optimizing Safety and Appropriateness of Graft Use in Transvaginal Pelvic Reconstructive Surgery

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Abstract
Introduction and hypothesis The recent rapid and widespread adoption of the use of mesh, and mesh-based surgical kits for pelvic organ prolapse (POP) repair surgery has occurred largely unchecked, and is now being subjected to critical analysis and re-evaluation.
Methods There have been multiple driving forces for this phenomenon, including aggressive marketing by surgical device manufacturing companies, contagious hype among pelvic surgeons and regulatory processes which facilitated relatively rapid marketing of new devices.
Results Patient-related factors such as indications for mesh use, expected risks and benefits relative to mesh implantation, and appropriately selected outcome measures have been slow to be defined.
Conclusions This manuscript reviews the currently available literature in the use of grafts and mesh in POP surgery with a focus on identifying situations where graft use may be appropriate for an individual patient. It also identifies specific clinical situations where mesh use may not be recommended.

Keywords Pelvic organ prolapse · Prolapse surgery · Mesh · Graft · Risk factors · Recurrence · Failure · Complications · Society recommendations · Indications

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Introduction

Over 300,000 prolapse procedures are performed annually in the USA [1]. Recent evidence suggests that mesh kits are being implanted with increasing frequency, although precise numbers are lacking. The expanding use of mesh kits is likely occurring due to widespread intensive marketing, ease of use with and increased surgeon training, and the perception that traditional vaginal pelvic floor repairs for urogenital prolapse have a poor long-term outcome.

The increased use of grafts, particularly using synthetic materials, in pelvic floor reconstruction has been associated with a greater awareness of the potential risks associated with their implantation. Thus, there is currently much controversy regarding the appropriate use of grafts in the pelvis

and the need for recommendations to guide surgeons in improving their surgical outcomes and reducing reported adverse events. The 2011 updated Food and Drug Administration Public Health notification concluded that "serious complications associated with surgical mesh for transvaginal repair of POP are not rare" and that "it is not clear that transvaginal POP repair with mesh is more effective than traditional non-mesh repair". One of the recommendations is to "choose mesh surgery only after weighing the risks and benefits of surgery with mesh versus all surgical and non-surgical alternatives." [2].

This article summarizes the scarce evidence currently available and provides usage recommendations based on literature and expert opinion. It resulted from an International Urogynecological Association-sponsored symposium convened to review the current state of transvaginal mesh use in pelvic reconstructive surgery and provide guidance to current and future pelvic surgeons and involved parties (professional societies, governing bodies, hospitals, patients, and patient organizations, etc.) for enhancement in safety and improved outcomes in prolapse surgery when mesh is used via the vaginal approach.

Looking at traditional repairs, the main problem rests in the huge number of surgical techniques described and the variations in the techniques from one surgeon to another. Most of the time, there is no consensus between surgeons and certainly no available data to achieve standardization in the traditional techniques for pelvic organ prolapse repair. This is true when analyzing surgical technique details, but even more important when assessing a surgeon's choice for a primary repair between traditional vaginal colporrhaphy, site-specific repair, vaginal obliteration, and even surgical suspensions with absorbable or non-absorbable sutures, such as paravaginal, uterosacral ligament, or sacrospinous ligament suspensions.

Most surgeons use some of these different techniques for various indications based on the different defects, the quality of the tissues, and the age of the patient. These choices are often made on a personal or local standard basis without scientific validation and most frequently without level 1 evidence

Conversely, mesh reinforcements are often pooled together in the different studies, and there is growing evidence that there are many material differences even considering only type 1 polypropylene mesh. The difference of weight of polypropylene, the way it is coated or not, the pore size, the different knitting, the total surface area of the polypropylene to be implanted, the rigidity, and the potential mesh elasticity, all could have consequences in terms of complications, mesh exposure rates, and especially mesh contraction, pain, and dyspareunia rates. The different kits, with their variety of suspension techniques, whether tension free, or with direct tensioned anchoring, will give different variations in anatomic results and potentially late complications.

This lack of standardization of traditional approaches and the huge variety of all the new kits available are a major problem for valid comparisons among these techniques.

The use of synthetic mesh has some potential benefits arising from past and current experience in hernia repair and female stress incontinence surgery. Most of these reported benefits are not proven and more studies are needed to confirm if there indeed is:

- surgical simplification with reduction in surgical times and a reduced surgical learning curve
- decreased short-term morbidity including postoperative pain compared to classical native tissue repair
- lower long-term recurrence rates
- actual benefit to the patient in terms of decreasing symptoms compared to native tissue repair

Do we currently have enough data from which to make mesh usage recommendations?

Recent years have seen a large number of publications regarding the use of grafts and mesh kits for prolapse repair. There have now been sufficient publications to allow systematic reviews and meta-analyses to be published [3, 4].

Unfortunately, most series have significant shortcomings:

1. Inclusion criteria are often poorly specified. Various degrees of prolapse are reported together with most series including primary as well as recurrent prolapse cases
2. Outcomes often include only anatomical factors. If functional outcomes are reported, they are limited to dyspareunia, urinary and defecatory dysfunction, occasionally pain, and rarely activities of daily living. Furthermore, if validated questionnaires were used, authors tend to report solely the overall scores making the interpretation of symptoms, like (persistent or de novo) overactive bladder and stress urinary incontinence and the development of pain, difficult
3. Native tissue repair controls are rarely included. Some trials have a native tissue repair arm that is frequently significantly different from the grafted arm—such as comparisons of anterior colporrhaphy without apical repair with four-armed mesh attached to the sacrospinous ligament
4. Most series include single and multisite-grafted repairs.
5. Apart from the use of defined mesh kits, the description of the employed mesh (especially outside of marketed kits), its properties, how it is tailored, where it is positioned and what it is attached or sutured to, is typically inadequate.

6. The methodology for reporting anatomic outcomes varies (i.e., overall pelvic organ prolapse (POP)-Q score vs. compartmental score, reporting of means vs. stages, etc.)
7. Follow up is usually short with most series reporting 1 year or less
8. Small case series. The largest reported study coming from the multicenter French TVM group including nearly 800 patients. However, most series include less than 200 patients
9. The learning curve of the surgeons enrolling patients in these studies is not always fully described or completed by all enrollers
10. If present, the control native tissue repairs are not always performed utilizing the same technique
11. Different inherent properties, including weave, elasticity, total surface area of the polypropylene, and weight of type 1 polypropylene is used in different kits, making compilations of case series inaccurate

Very few published papers provide level 1 evidence regarding transvaginal mesh use for POP. Thus, there is clearly a need for well-run and properly monitored registries. Given that a meta-analysis of randomized controlled trials is considered the highest level of evidence, the updated Cochrane review on the surgical management of pelvic organ prolapse [5] and the recent systematic review including other study designs [4] are summarized here regarding vaginal pelvic organ prolapse graft or mesh repairs to present the current status of available studies and their limitations.

In the anterior compartment, biological graft or synthetic mesh are better than no mesh or graft, and synthetic mesh is better than biological graft in terms of objective failure in the anterior compartment [4]. The Cochrane review determined that any non-absorbable synthetic mesh implantation (inlay, overlay, or armed meshes) improves the anatomical outcome [5]. However, there are no appropriate studies to be able to provide advice on different coatings or weaves of type I polypropylene mesh or on different mesh kits. Also, there are not enough randomized trials to recommend certain biological grafts, although bovine pericardium collagen matrix [6] and solvent dehydrated cadaveric fascia lata [7] repairs were similar to native tissue anterior repair. Only Pelvicol proved better in one small trial [8]. Although anatomical outcomes may be better with the use of grafts or mesh, this has not been shown to be applicable to functional outcomes. If quality of life questionnaires were used, there were no differences in any randomized trials. The same is true for rates of de novo dyspareunia and stress urinary incontinence [5].

In the posterior compartment, there was only one randomized trial demonstrating that porcine small intestine submucosa graft inlay, as well as posterior colporrhaphy or site-specific posterior repair improves functional outcomes including bowel symptoms, quality of life, and sexual function. However, grafted anatomical outcomes were not superior to native tissue repair [9].

The appalling lack of information on functional outcomes is inadvertently illustrated in a review by Jia et al. Anterior repair objective outcome was reported in more than 1,000 women who received biological grafts and in more than 500 who received synthetic mesh whereas functional outcome was described in only 14 and 44 women, respectively [4].

Aside from randomized controlled trials and other prospective trials, there are valuable studies analyzing complications like mesh exposure and risk factors like body mass index (BMI), concurrent hysterectomy, age, and smoking. Also, many of the studies and series do have similarities, which allow observations to be based on the compiled data presented. Interpretation by surgical experts can help to put the expanding published literature in perspective and may help to make recommendations based on expert opinion in addition to the publications to date. The format of this Roundtable allowed us to receive input from all of the participating surgeons, many of who had performed over 300 grafted/kit operations. Thus, the recommendations given are based on a combination of data, its interpretation, and expert experience and opinion.

Terminology for recommendations

Since there are many reported ways of correcting prolapse, and great variation in individual patient characteristics, we felt the term "indication" was too strong and would suggest that other grafted or nongrafted approaches (i.e., paravaginal repair, posterior colporrhaphy) would not be appropriate for a given patient. Until there have been properly conducted controlled studies comparing grafted/kit repairs to more traditional nongrafted repairs, more conclusive statements cannot be made. Thus, we opted to use terminology, which stratifies the degree of expected impact on the patient's surgical outcome:

1. likely to be beneficial
2. possibly beneficial
3. unlikely to be beneficial
4. not recommended

The final category—not recommended—is designed to dissuade surgeons from using a graft in a patient where the recognized potential risks may significantly outweigh any benefit to the patient. We opted to include both synthetic mesh and biologic grafts. Although there are only a few kits which include biologic grafts, there is a significant volume of data on cross-linked as well as noncross-linked grafts for

prolapse correction. We did not go as far as attempting to recommend a synthetic over a biologic graft for a specific clinical situation, but do differentiate implantation techniques and other factors in Table 1.

Individual patient factors (host)

We considered various host factors when making recommendations regarding mesh/graft use. The assumption was made that all synthetic mesh would be light-weight type 1 polypropylene.

- Age—the cutoff is clearly very arbitrary. The age of 50 is based on life expectancy, physical activity level, and likelihood of regular sexual activity. Also, the onset of menopause is known to negatively impact on the collagen I/III ratio [10, 11]. However, a healthy 60 year old who is sexually active on a regular basis may have personal characteristics more like a younger woman. Thus the age cutoff for mesh/graft use needs to be individualized. There is evidence that the exposure rate increases by 2.2-fold in women over the age of 60 years [12], but many other studies do not confirm these data
- Recurrent prolapse. This should be clearly differentiated from primary prolapse as recurrence rates when scarred and/or deficient fascia is used are greater than when site-specific repairs can be performed with healthy, unscarred fascia [13, 14] The vast majority of papers do not differentiate between included primary vs. recurrent POP cases. Surgeons have begun to recognize this factor and studies report evaluating the outcomes of traditional vs. grafted surgery in this particular group of patients [15]
- Site and stage of prolapse—anterior, apical, posterior. There are clear differences in incidence, severity, and recurrence rates of prolapse in different vaginal compartments. Anterior compartment prolapse is more prevalent [16] and more prone to failure after repairs [17]. Advanced cystoceles are often associated with apical support defects [18]. This inter-relation has implications regarding repair of anterior wall prolapse and thus must be taken into account. We separated the compartments into apex/uterus, anterior and posterior based on current approaches to prolapse correction. Higher stages of preoperative POP are also recognized to be associated with higher rates of recurrence.
- Collagen deficiency and other tissue factors—(i.e., hypermobility, laxity, poor quality fascia). There are currently no objective clinical means of describing quality of the fibromuscular vaginal wall layer. However, this factor is very important in achieving a successful anatomic correction, especially if native tissues are utilized. Since mesh/grafts are intended to replace or reinforce this vaginal wall fibromuscular layer (a.k.a. fascia), it is important to take this factor into account when considering graft use. In addition, other soft tissue factors such as enlarged levator hiatus, levator muscular avulsion, and weak pelvic floor musculature are increasingly recognized as risk factors for POP recurrence. The association between Ehlers Danlos or Marfan's syndrome [19] and joint hypermobility [20, 21] has long been described. We opted to use the description of "deficient fascia" as a variable for mesh use.
- Chronic and/or repetitive increases in intra-abdominal pressure (a.k.a. chronic pelvic floor stress, i.e., chronic cough or Valsalva), especially when sudden, are associated with the development of prolapse and its recurrence after surgical repair. This category represents any condition associated with chronic increases in intra-abdominal pressure, e.g., chronic constipation which is a known risk factor for pelvic organ prolapse [22, 23]. Occupational heavy lifting is another factor that should be considered [24, 25].
- Presence of and/or history of systemic or localized pelvic pain or dyspareunia. Post-operative vaginal and pelvic pain—following grafted or native tissue repair—represents a difficult, frustrating condition to understand and treat. Following a grafted repair, the patient may attribute any persisting or de novo pain to the implanted graft. However, the pain may be neuromuscular in nature. There is no guarantee that removal of an implanted graft will result in resolution of the pain. In addition, removal of an entire graft may predispose the patient to recurrent prolapse and a yet more challenging repair. Although our understanding of pelvic pain is poor, the main risk factor for the development or persistence of problematic post-operative pain is the presence of pain pre-operatively [26]. Systemic pain syndromes such as fibromyalgia are extremely poorly understood. The pain may be exacerbated by any intrinsic or extrinsic stimulus. Recovery is delayed and sometimes protracted. Pelvic surgery itself may exacerbate systemic pain. The presence of a graft may just be an additional noxious stimulus.
- Pregnancy. This includes the possibility of future pregnancies. There is no reported data regarding pregnancy in women who have undergone transvaginal graft implantation for pelvic organ prolapse. Thus, this situation should be avoided.

Additional factors to be considered include:

- Genital atrophy. Vaginal atrophy may make surgical dissection more challenging and increase the risk of healing problems. It should be treated pre-operatively with local vaginal estrogen preparations.
- Diabetes mellitus. Especially when blood sugar is not well controlled, tissue healing may be impaired and may

Table 1 Potential benefits of graft use for vaginal prolapse

Variable	Likely benefit	Possible benefit	Unlikely benefit	Not Recommended
Age				
a <50			✓ S, B	
b ≥50		✓ S, B		
Recurrent (same site)		✓ S, B		
Cystocele/Anterior compartment				
a ≥st 2		✓ S, B		
b <st 2				✓ S, B
Posterior compartment			✓ S, B	
Apex (vault, cuff, cervix)		✓ S	✓ B	
Deficient fascia		✓ S, B		
Chronic increase intra-abdominal pressure		✓ S, B		
Pain syndromes: local/systemic				✓ E, O
Possibility of pregnancy				✓ E, O
Combination of factors				
Recurrent + cystocele>st. 2	✓ S, B			
Recurrent + posterior compartment		✓ S, B		
Recurrent + apex/cuff/cervix	✓ S		✓ B	
Recurrent + increased intra-abdominal pressure	✓ S, B			
Recurrent + deficient fascia	✓ S, B			
Cystocele>st. 2 + increased intra-abdominal pressure	✓ S, B			
Cystocele>st. 2 + deficient fascia	✓ S, B			

S synthetic, *B* biologic, *E* evidence, *O* expert opinion

increase the likelihood of graft exposure if synthetic material is used.

- Steroid use. Chronic or acute high dose steroid use may affect tissue healing by increasing skin fragility, impairing collagen synthesis and reducing skin vascularity. Local estrogen therapy may have a beneficial effect in these patients. If a synthetic graft is used in these patients, it should be undertaken with caution.
- Smoking. Smoking, as with any plastic operation involving a skin flap, is associated with an increased risk of mesh exposure, likely due to reduced vascularity [26]. In one series, the risk of exposure was increased 3.7-fold in smokers [12].
- BMI. Apart from being a risk factor for pelvic organ prolapse in epidemiological studies [27, 28], an increased BMI has been associated with an increased risk of mesh exposure and wound infection [29]. In one series, the risk of exposure increased 10.1-fold in women with a BMI>30 [12].
- Concurrent hysterectomy. If a vaginal hysterectomy is performed, especially if a T incision results at the vaginal cuff from an anterior wall incision, the risk of mesh exposure increases significantly [30–32].

In addition to patient factors to be considered when determining the appropriateness of mesh implantation, there are various *technical factors*, which should be taken into account:

- Apical/uterine prolapse. Advanced degrees of vaginal prolapse, especially of the anterior compartment, are frequently associated with apical and/or uterine descent. It is debatable whether or not mild degrees of apical/uterine prolapse in association with significant anterior or posterior wall prolapse needs to be routinely addressed. Certainly, the presence of apical prolapse≥stage 2 should be corrected surgically. If there is an associated large anterior vaginal wall defect as well, consideration should be given to repairing lesser degrees of apical descent. The management of this common anatomic alteration needs to be individualized.
- Tensioning. Synthetic mesh is known to shrink after implantation due to collagen in-growth. In order to avoid "mesh bands", and optimize vaginal wall elasticity, the mesh should be left on minimal tension during implantation. Surgeons should resist the temptation to place the mesh "snuggly". Care should be particularly placed to the strain placed on mesh arms. In addition, rectal compression should be avoided when a posterior mesh is implanted.
- Depth of implantation. Experience with the use of synthetic mesh has led to the development of

specific surgical techniques including hydrodissection of the subfascial plane and deep mesh implantation. Deeply implanted synthetic mesh is used to replace deficient fascia. When a synthetic mesh is placed as an overlay to fascial plication, the risk of exposure increases significantly [33, 34]. When a mesh has been implanted correctly in the appropriate tissue plane, the graft should not be easily palpable. When biologic grafts are used, the risk of exposure is minimal, and the graft may be used to reinforce plicated fascia as an overlay [35].

- Management of excess vaginal epithelium. Increasing knowledge regarding the shrinkage of synthetic mesh after implantation has highlighted the fact that care must be taken to limit any trimming of the vaginal epithelium, in order to minimize the risk of vaginal stricture formation and resultant dyspareunia.
- Surgeon experience. Years of experience in prolapse repair has been shown to be inversely related to the risk of mesh exposure [26].
- Choice of materials. There are inherent and critical differences between synthetic and biologic materials available for implantation. It has become increasingly apparent that of the synthetic mesh choices, only lightweight type 1 polypropylene should be used. However, it must be recognized that all type 1 polypropylene meshes are not the same due to construction differences including weave, weight, management of mesh edges, etc. Subtle differences in mesh construction may have marked differences in clinical outcomes. It is hoped that no other untested synthetic mesh materials are currently being used clinically.

Biologic materials may be of human or animal origin. Their post-implantation behavior is determined by the preparatory chemical treatment. Collagen bonds are either fixed (unable to be broken down by host enzymes) during chemical cross-linking, or broken down over time if the material is noncross-linked. The purpose of cross-linked material is to be present permanently, while noncross-linked materials act as a collagen and vascular in-growth matrix after implantation and are gradually broken down over a number of months by host enzymatic activity. Biologic grafts are typically implanted as an overlay to plicated fascia, and thus reinforce (rather than replace) endogenous fascia. Complication rates (including exposure, contraction, and other healing abnormalities) with biologic materials are significantly lower than those found with synthetic materials.

- Associated stress urinary incontinence (SUI)/occult SUI. The management of stress incontinence—whether symptomatic or occult—in a woman with significant prolapse is an area of marked controversy. Whether the stress incontinence should be managed at the same time as the prolapse (concomitant repair) or in a subsequent outpatient procedure (sequential surgery) is unclear. In the Cochrane review, two small trials [36, 37] included women with occult SUI who significantly benefited from a tension-free vaginal tape in addition to an anterior repair. Until more data are available, patients with significant prolapse should be carefully screened for SUI and after discussion between the healthcare professional and the patient, a decision should be made whether to treat both at the same time or undertake the prolapse surgery in the first instance and if the SUI persists, accept the need for further surgery at a future date.

In order to draw valid conclusions and give recommendations that are based more on data than on expert opinion, in future surgical studies involving grafts or mesh investigators should consider the following issues:

- Inclusion of a native tissue repair arm that really is comparable to the graft repair (e.g., concurrent apical repair when armed graft is used)
- Inclusion of validated symptom and quality of life questionnaires
- Report of functional outcome of all compartments (bladder, bowel, sexual function, prolapse symptoms) and pain syndromes
- Inclusion of patient-related and centered outcome instruments
- Stratification of primary and recurrent pelvic organ prolapse repair
- Outcome analysis considering risk factors like BMI, age, smoking, etc.

Summary

Increasing availability of mesh kits together with expanding surgical experience have dramatically increased mesh use in vaginal prolapse surgery despite the fact that the available data are severely limited. Most of the publications to date would suggest improved objective surgical outcomes but with a significant complication rate in all reported series including pain, dyspareunia, and graft exposure. To date, we do not have sufficient information regarding patient selection to adequate counsel patients regarding the risk:benefit ratio of mesh repair versus native tissue repair. Thus, we urgently need high-quality research to address the problems that we have encountered to date and to enhance our ability to develop definitive guidelines regarding the use of mesh. However, for the preparation of these recommendations, we

were able to identify—and agree upon—specific circumstances where the use of mesh may be appropriate as long as the patient is fully aware of the possible outcomes.

Conflicts of interest G. Willy Davila is a speaker, consultant, and grant recipient of Astellas, CL Medical, and AMS, and a consultant for Coloplast, Teva, and Israel Biomedical Innovations. Michel Cosson is a lecturer and has a patent in process with Ethicon, has a patent in process with Cousin Biotech, and is a lecturer at Ipsen and Olympus. Linda Cardozo is a speaker, consultant, or researcher at Pfizer, Astellas, and Teva. Dr. Kaven Baessler has no conflict of interest.

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