A prospective randomized trial comparing Restorelle® Y mesh vs. Vertessa® lite Y mesh for laparoscopic and robotic-assisted laparoscopic sacrocolpopexy

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Background and Significance:

Abdominal sacrocolpopexy is considered the gold standard for vault prolapse, and has demonstrated superior anatomic outcomes compared to transvaginal suspension procedures. Laparoscopic sacrocolpopexy has become an alternative to open abdominal sacrocolpopexy as this mode of surgery bridges the gap between the advantages of vaginal surgery, namely decreased morbidity and faster patient recovery, with the surgical success rates of abdominal sacrocolpopexy (1). For young women who are sexually active with symptomatic pelvic organ prolapse, reconstruction with a sacrocolpopexy procedure is beneficial because the success rates are high as the procedure adequately restores support of the vaginal apex and maintains vaginal length (2). Robotic-assisted laparoscopic sacrocolpopexy has also emerged as a mode of vaginal vault prolapse surgery, and is a good option for patients with significant body mass index, or known pelvic adhesive disease that may make a conventional laparoscopic approach more challenging.

Sacrocolpopexy involves suspension of the vagina to the anterior longitudinal ligament of the sacrum at the level of S1 using a bridging graft which can be made of biologic or synthetic materials. The graft is sutured to the anterior as well as the posterior vagina and then attached to the anterior longitudinal ligament of the sacrum. There are a number of prosthetic materials available for use in pelvic reconstructive surgery, including sacrocolpopexy. Mersilene was a popular prosthetic for many decades, but its use rapidly declined in favor of polypropylene which is now the most commonly used synthetic product (3). The ideal prosthetic material is biocompatible, inert, has minimal allergic or inflammatory reaction, is sterile, non-carcinogenic, resistant to infection, and avoids shrinkage and mechanical stress and is easy to handle and readily available at a reasonable cost (4). Additionally, pore size of the graft material affects resistance to infection and cellular infiltration and also the flexibility of the mesh (5). Lastly, the interaction at the tissue interface of the graft material is also very important, with the ideal prosthesis causing minimal initial inflammatory and cellular response followed by adequate vascular and fibroblastic infiltration (6). Many different materials have been used as a graft in sacrocolpopexy including biologic materials (fascia lata, rectus fascia, dura mater) and synthetic materials (polypropylene mesh, polyester fiber mesh, polytetrafluorethylene mesh, Dacron mesh, and Silastic silicone rubber). Large pore light-weight polypropylene mesh is a monofilament graft and is most commonly used

today as it meets the above-mentioned requirements, and likely has fewer complications compared to other synthetics because of these characteristics (2). Both the Restorelle® Smartmesh (Coloplast, Inc., Minneapolis, MN, USA) and the Vertessa® lite mesh (Caldera Medical. Inc., Agoura Hills, CA, USA) are ultra-light macroporous polypropylene mesh grafts that are intended for pelvic floor reconstruction. Currently, both types of grafts are used to perform sacrocolpopexy.

In our urogyneoclogy practice at Cleveland Clinic, we currently routinely use the Restorelle® Smartmesh and we have experienced good clinical outcomes using this graft. This mesh seems to have been widely adopted by many surgeons performing sacrocolpopexy. To our knowledge, the only prospective study that exists looking at this mesh at the time of sacrocolpopexy was published by Salamon et al. (7) in 2013 in the International Urogynecology Journal. In this study, the authors sought to prospectively evaluate the use of Restorelle® Y mesh for robotic sacrocolpopexy. They implanted a total of 120 patients and obtained one year follow-up data from 118 of these patients. They reported an anatomic success rate of 89%, a subjective cure rate of 94% and no mesh erosions. Currently no prospective data exists on the Vertessa® lite mesh for sacrocolpopexy. It is used by many surgeons, but there are no data showing that it is as efficacious in treating prolapse and avoiding mesh erosion in those patients undergoing sacrocolpopexy. Therefore, the primary objective of the proposed study is to compare outcomes between the Restorelle® Y mesh and Vertessa® lite Y mesh at the time of laparoscopic and robotic-assisted laparoscopic sacrocolpopexy.

Hypothesis: Vertessa® lite Y mesh is not inferior to Restorelle® Y mesh for the treatment of vaginal vault prolapse.

Study Design: Randomized single-blind non-inferiorty trial

Primary Outcome:

Composite outcome measure of surgical success:

(1) descent of the vaginal apex more than one-third into the vaginal canal
(2) anterior or posterior vaginal wall descent beyond the hymen
(3) bothersome vaginal bulge symptoms
(4) retreatment for prolapse by either surgery or pessary

Secondary Outcomes:

1. Intraoperative, peri-operative and post-operative complications
2. Pelvic floor symptoms (urinary, bowel, prolapse, sexual function): PFDI, ISI, PISQ)
3. Retreatment for urinary incontinence

Study Population: Study subjects will be recruited from patients that present to the Center for Urogynecology & Pelvic Reconstructive Surgery in the Department of Obstetrics and Gynecology at the Cleveland Clinic Main campus, Hillcrest Hospital and Fairview Hospital, and their surgeries will be performed at either one of these sites.

Inclusion Criteria:

- Age ≥ 18, who are to undergo laparoscopic or robotic laparoscopic sacrocolpopexy for pelvic organ prolapse
- Other concomitant laparoscopic or prolapse and anti-incontinence procedures (e.g., laparoscopic supracervical hysterectomy, cystocele repair, rectocele repair or mid-urethral sling procedures) will be performed at the primary surgeon's discretion.

Exclusion Criteria:

- Inability to comprehend written and/or spoken English
- Inability to provide informed consent
- Medical illness precluding laparoscopy
- Need for concomitant surgeries not related to pelvic organ prolapse or incontinence
- Sacrocolpoperineopexy
- Need for dual flat mesh for sacrocolpopexy procedure (determined by surgeon)

Study Procedures:

Study Identification and Recruitment

Potential subjects will be identified by members of the Center for Urogynecology & Pelvic Reconstructive Surgery at the Cleveland Clinic Main campus and Fairview Hospital. Eligible patients that agree to participate will be provided written informed consent administered by the collaborators listed on this IRB.

Randomization

All subjects will be predetermined by their surgeon to undergo either a laparoscopic or robotic assisted laparoscopic sacrocolpopexy depending upon their clinical evaluation. The participants will then be randomized to either Restorelle® or Vertessa® Y sacrocolpopexy according to a computer-generated randomization schedule with random block sizes with the use of the SAS statistical software package (SAS Institute, Cary, NC). All patients will be blinded to their assignment.

Office Interventions

All patients will be seen for a preoperative visit and then postoperatively at 6, 12 and 24 months. At each visit, a vaginal exam and a complete Pelvic Organ Prolapse Quantification (POP-Q) exam will be performed. Patients will also be asked to update their medical history. In addition, patients will be asked to complete the Pelvic Floor

Distress Inventory (PFDI-20), Incontinence Severity Index (ISI) and Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) questionnaires at the pre-operative visit as well as the 6, 12, and 24 month postoperative visits. Completion of these questionnaire is the only additional assessment that is specific to participation in this study and is not usually included as part of the standard care of sacrocolpopexy. It should take no more than 10-15 minutes to complete the questionnaires. The study subjects will not be exposed to any additional risk by participating in this study except for the inconvenience of completing the questionnaire.

Surgical Interventions

Laparoscopic sacrocolpopexy will be performed using four ports: an umbilical port for the laparoscope, two ports (either 5 or 10/12 mm) in the bilateral lower quadrants, and one 5-mm port placed at the level of the umbilicus, lateral to the rectus muscle on either side for retraction. The robotic-assisted hysterectomy will be performed using the da Vinci Surgical System (Intuitive Surgical Inc., Sunnyvale, CA, USA) using five ports: a 12mm umbilical port for the laparoscopic, two 8 mm robotic ports placed 2cm inferior and 9-10cm lateral to the umbilicus bilaterally, an 8mm robotic port placed in the left axillary line at the level of the umbilicus, and a 8mm or 10/12mm accessory port either in the right upper quadrant approximately 3cm distal from the costal margin, or in the right lower quadrant, 2cm above and medial to the anterior superior iliac spine.

If a supracervical hysterectomy is to be performed, it will be done in a standard fashion. A uterine manipulator will be placed inside of the uterus. The round ligaments will be transected using cautery. The fallopian tubes and ovaries will be left in situ or removed at the time of hysterectomy depending upon the preoperative decision made between the surgeon and patient. The uterine arteries and cardinal ligaments will be cauterized laparoscopically. The uterus will be amputated at the level of the internal cervical os and the endocervical canal will be cauterized.

The sacrocolpopexy will also be performed and in a standard fashion. An end-to-end anastomosis (EEA) sizer will be placed in the vagina for manipulation of the apex as well as in the rectum for delineation of the rectovaginal septum. First, the presacral dissection will be performed with a longitudinal peritoneal incision over the sacral promontory and there is identification of the anterior longitudinal ligament. Dissection is then done caudally through the peritoneum and subperitoneal fat down to the level of the posterior cul-de-sac. The vagina is elevated cephalad using the EEA sizer and the peritoneum overlying the anterior vaginal apex is incised transversely, and the bladder is dissected off the anterior vagina using sharp dissection, creating a 4 to 5 cm pocket. If this plane is difficult to establish, the bladder will be filled in a retrograde fashion to find the correct dissection plane. Similarly, the peritoneum overlying the posterior vagina is incised, and dissection is then done overlying the vagina and extending into the posterior cul-de-sac, creating a 4 to 5 cm pocket. Once dissection is complete, the mesh graft is prepared. Subjects will have been randomized to either one of two mesh grafts:

The Y mesh is introduced into the pelvis through one of the ports. First, either then anterior or the posterior arm is fixed to the anterior or posterior vaginal wall using 6

delayed- absorbable (PDS) No. 2-0 sutures in an interrupted fashion, 1 to 2 cm apart from each other. The opposing arm of the graft is then attached to either the anterior or posterior vaginal wall, depending on which arm was placed first, in a similar fashion using 6 delayed- absorbable (PDS) No. 2-0 sutures in an interrupted fashion, 1 to 2 cm apart from each other. The stem portion of the graft is then brought to the sacral promontory and sutured to the anterior longitudinal ligament using 2 permanent (prolene) No. 0 sutures. The excess mesh is then trimmed.

The peritoneum is then closed over the exposed graft with absorbable suture.
Routine cystoscopy will also be performed in order to assess for lower urinary tract injury. A vaginal exam is performed, and an anterior and/or posterior colporrhaphy and perineorrhaphy are performed if needed. Anti-incontinence procedures may also be performed if needed.

**In laparoscopic cases, all suturing will be done extracorporeally while intracorporeal knot-tying technique will be performed in robot assisted laparoscopic cases.

<u>Data Collection & Management</u>:

Preoperative data will include the following:

- Patient age, race, vaginal parity, menopausal sate, BMI, prior prolapse surgery, preoperative prolapse stage
- PFDI-20, ISI, PISQ-12
- Preoperative hemoglobin

Data points recorded during the procedure will include:

- Total OR time = operating room time of entry and exit
- Total Case time = time from incision to closure
- Concomitant procedures
    - Supracervical hysterectomy
    - Anterior colporrhaphy
    - Posterior colporrhaphy
    - Perineorrhaphy
    - Midurethral sling
- Estimated blood loss
- Intraoperative complications
    - EBL > 500cc
    - Vascular Injury
    - Cystotomy
    - Ureteral Injury
    - Bowel Injury - small bowel, large bowel, rectal

Postoperative data will include the following: 6, 12, 24 months

- POP-Q exam (performed by a provider blinded to the mesh used at the time of the procedure)
- PFDI-20, ISI, PISQ-12

- Review of electronic medical record (inpatient notes, d/c summary, ER visits), assessing for postoperative complications
    - Reoperation for immediate complications = reoperation within 30 days of surgery
    - Abdominal Wound infection = fascial, subcutaneous, cutaneous infection requiring antibiotic treatment
    - Hematoma = intrapelvic/abdominal
    - Vaginal cuff cellulitis/Pelvic Abscess = requiring IV/PO antibiotic therapy and/or transvaginal, trangluteal or percutaneous drainage
    - DVT/PE = diagnosed with Doppler US or CT scan
    - Reoperation for SUI with pubovaginal sling (synthetic or fascial), colposuspension, injection with periurethral bulking agents
    - Reoperation for mesh exposure
    - Reoperation for recurrent POP
    - Bowel Injury/Bowel Obstruction = enterotomy, perforation, ileus, partial/complete obstruction
    - Port site or incisional hernia
    - Need for any radiologic imaging
    - Lower urinary tract injury = bladder, ureteral
    - Neurologic Injury = brachial plexus, abdominal wall (ilioinguinal, iliohypogastric), lower extremity (femoral, sciatic, common peroneal)
    - Pulmonary complications = pneumonia, pulmonary hypertension, pulmonary edema within 14 days of surgery
    - Cardiac = ACS, MI, HF within 14 days of surgery
    - Postoperative ICU admission

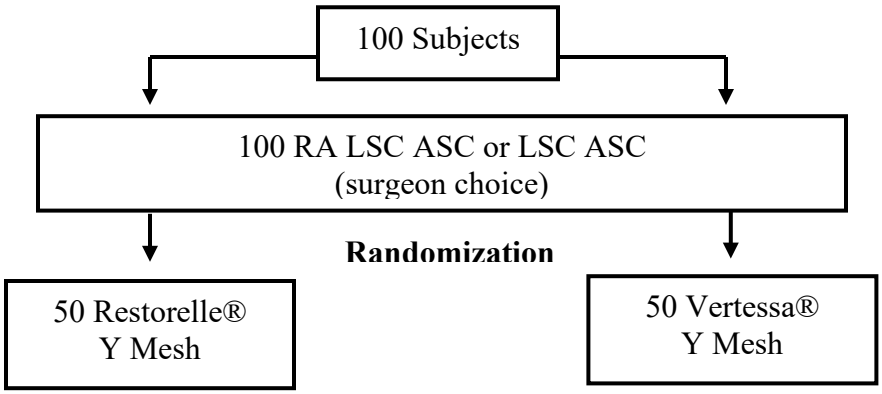
Protection of each subject's personal health information will be a priority in this study. One master excel file containing subject personal information including name and medical record number will be kept in a password-protected file, on a designated protected research drive on a password-protected computer in a locked office at the Cleveland Clinic. In that file, each subject will be assigned a subject identification number that will be used for the purposes of data collection in order to de-identify subjects.

All paper forms used for data collection will be kept in a research cabinet dedicated to this project which will be locked at all times, in a locked office at the Cleveland Clinic. All forms will contain de-identified information – identification numbers will correspond to the subjects listed in the master excel file.

All study data will be transferred and managed electronically using REDCap (Research Electronic Data Capture). Each subject will be entered into REDCap using the assigned identification number from the master excel file. REDCap is a secure, web-based application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation, audit trials, and a de-identified data export mechanism to common statistical packages. They system was developed by a multi-institutional consortium which was initiated at Vanderbilt University and includes the Cleveland Clinic. The database is hosted at the Cleveland Clinic Research Datacenter in the JJN basement and is managed by the Quantitative Health Sciences Department. The system is protected by a login and Secure Sockets Layers (SSL) encryption. Data collection is customized for each study as based on a study-specific data dictionary defined by the research team with guidance from the REDCap administrator in Quantitative Health Sciences at the Cleveland Clinic.

Analysis Plan:

There will be 2 arms to this study: laparoscopic (robotic-assisted and conventional) sacrocolpopexy with Restorelle® Y mesh and laparoscopic (robotic-assisted and conventional) sacrocolpopexy with Vertessa® Y mesh. Subjects will be chosen based on surgeon preference to either undergo RA LSC ASC or conventional LSC ASC. They will then be randomized to either the Restorelle® or Vertessa® Y mesh arm. We determined that if there is no difference between the two Y mesh grafts, 90 patients are required to be 70% sure that the upper limit of a one-sided 95% confidence interval will exclude a difference in favor of the Restorelle® group of more than 10%. We will account for a potential 10% subject drop out and loss to follow-up as well as unforeseen factors in recruiting and will plan to recruit 50 subjects to each arm, for a total of 100 subjects.



All statistical analyses will be done using jmp 12. We will use descriptive statistics to show our demographic and baseline data: categorical variables will be presented as n/N (%) with 95% confidence intervals and continuous variables will be presented as mean +/-SD [range]. The two Y mesh grafts will be compared. Differences between the groups in the primary outcome of surgical success and other categorical outcomes were evaluated using generalized linear models. We will control for LSC ASC and RA LSC ASC by performing a logistic regression.

Summary of tasks for study:

	Preop	6 mo	12 mo	24 mo
Informed consent	X			
Demographic data	X			
Randomization	X			
PFDI-20	X	X	X	X
ISI	X	X	X	X
PISQ-12	X	X	X	X
POP-Q	X	X	X	X
Review of d/c summary, chart, postop Hct, complications (ER visits, etc)		X		
Update medical history		X	X	X

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