A prospective randomized trial comparing restorelle Y mesh vs. restorelle dual flat 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).

Restorelle Smartmesh (Coloplast®, Minneapolis, MN, USA) is an ultra-light macroporous polypropylene mesh graft intended for pelvic floor reconstruction. Two grafts are currently made for sacrocolposuspension: the restorelle Y mesh and the restorelle flat mesh (L mesh). The Y mesh has two arms which attach to the anterior and posterior vagina and a stem which attaches to the sacral promontory. The flat mesh is a sheet of polypropylene that comes in three sizes (Restorelle M Flat Mesh - 15cm x 10cm, Restorelle L Rectangle Flat Mesh - 24cm x 8cm, Restorelle XL Flat Mesh - 30cm x 30cm) and can be trimmed into two strips that are attached to the anterior and posterior vagina, respectively, and then sutured together to the sacral promontory. Currently, both types of grafts are used to perform sacrocolpopexy.

Cost of health care has become a hot topic in the medical community. One of the focuses of cost containment in medicine has centered around operating room efficiency. Several studies have looked at OR time nonutilization (7) in order to determine the economic value of saving OR time. Surgeons can make significant contributions to these types of savings by reducing equipment needs, facilitating case set-up times, and focusing on intraoperative efficiency. This includes choosing materials that may make certain procedures faster and more efficient. When performing a sacrocolpopexy, surgeons have the option of choosing a mesh graft configured in a Y shape, which requires introduction into the pelvis only once, and suturing of one arm to the sacral promontory; versus a dual flat mesh, which requires introduction into the pelvis twice, as there are two separate pieces to suture to the vagina, and suturing of both pieces of mesh together to the promontory. It is unclear if one version of the restorelle mesh is faster to use than the other, and if this savings in time, translates to cost savings in the operating room. The primary objective of the proposed study is to determine the difference in suturing time when using the restorelle Y mesh versus the restorelle dual flat mesh at the time of laparoscopic and robotic-assisted laparoscopic sacrocolpopexy.

Hypothesis: Suturing time when using the restorelle Y mesh will be faster than when using the restorelle dual flat mesh at the time of laparoscopic and robotic-assisted laparoscopic sacrocolpopexy.

Study Design: Randomized single-blind prospective clinical trial

Primary Outcomes:

1. Total Suturing time for mesh placement = time from insertion of Y mesh or first flat mesh arm into pelvis to last sacral suture placed
2. Total OR time = operating room time of entry and exit
3. Total Case time = Incision to end of closure

Secondary Outcomes:

1. Intraoperative, peri-operative and post-operative complications
2. Hospital costs (Y mesh v. dual mesh and stratified by RA LSC v. LSC)
3. Post-operative patient outcomes at 6 weeks, 6 months, 12 months and 24 months
    - Pelvic Organ Prolapse Quantification (POPQ) system (standardized quantification of prolapse established by the International Continence Society) – Required at 6 months; Optional but encouraged at 12 and 24 months.
    - Pelvic Floor Dysfunction Inventory (PFDI-20) – Required pre-operatively and at 6 weeks, 6, 12 and 24 months.

Study Population: Study subjects will be recruited from patients that present to the Center of Urogynecology and Pelvic Floor Disorders 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 $\geq$ 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

Study Procedures:

Study Identification and Recruitment
Potential subjects will be identified by members of the Center for Urogynecology and 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 at the Cleveland Clinic main campus and Fairview Hospital.

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 Y mesh or dual flat mesh 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). Randomization will be carried out by provider. All patients will be blinded to their assignment.

Office Interventions
In addition to a standardized evaluation including the history and physical examination, patients will be asked to complete the Pelvic Floor Distress Inventory (PFDI-20) questionnaire at the pre-operative visit as well as the 6 week, 6, 12 and 24 month postoperative visit. 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 questionnaire. 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:

1. Restorelle Y mesh
    - The 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 5 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 5 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.

2. Restorelle dual flat mesh: 2 pieces of 15 x 4 cm mesh
    - One mesh arm is introduced into the pelvis through one of the ports.
    - The arm is fixed to the anterior or posterior vaginal wall using 5 delayed-absorbable (PDS) No. 2-0 sutures in an interrupted fashion, 1 to 2 cm apart from each other.
    - The second mesh arm is then introduced into the pelvis through one of the ports.
    - The arm is fixed to either the anterior or posterior vaginal wall, depending on where the first arm was placed, using 5 delayed- absorbable (PDS) No. 2-0 sutures in an interrupted fashion, 1 to 2 cm apart from each other.
    - The two arms are then brought to the sacral promontory and sutured together 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.

Data Collection & Management:

Preoperative data will include the following:

- Patient age, race, vaginal parity, menopausal sate, BMI, prior prolapse surgery, preoperative prolapse stage
- PFDI-20
- Labs (Hb/Hct)

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
- Total Suturing time = time from insertion of Y mesh or first flat mesh arm into pelvis to last sacral suture placed
- Level of surgeon performing suturing: Attending v. Fellow v. Both
- Concomitant procedures
    - Hysterectomy – Supracervical or Total
    - 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:

- Days in the hospital
- 6-week postoperative visit: PFDI-20
- 6-month postoperative visit (Required): POP-Q exam (performed by a provider blinded to the mesh used at the time of the procedure)
- 12 month, 24 month postoperative visit (Optional): POP-Q exam (performed by a provider blinded to the mesh used at the time of the procedure)
- 6-month, 12-month, 24-month postoperative visit: PFDI-20

- At 6, 12 and 24-months: 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

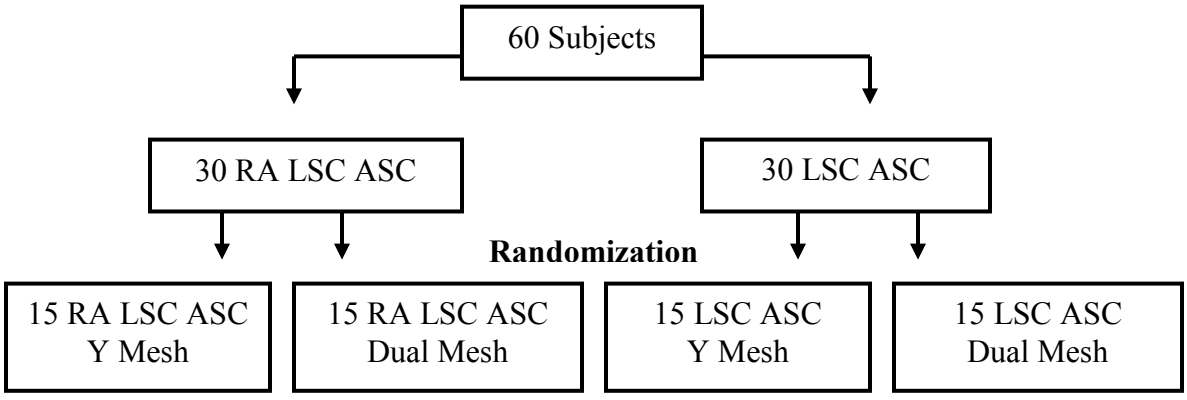
Protection of each subject's personal health information will be a priority in this study. One master excel file containing subject personal information including name and medical record number will be kept in a password-protected file, on a designated protected research drive on a password-protected 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 4 arms to this study: laparoscopic (robotic-assisted and conventional) sacrocolpopexy with Y mesh and laparoscopic (robotic-assisted and conventional) sacrocolpopexy with dual flat 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 a Y mesh arm or a Dual Mesh arm. We determined that 9 subjects in each arm were needed to detect a difference of 30 minutes or more in suturing time between the two groups with 80% power and a significance level of .05. We will account for potential subject drop out and loss to follow-up as well as unforeseen factors in recruiting and will plan to recruit 15 subjects to each arm, for a total of 60 subjects.



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]. Y mesh and dual mesh will be compared between the two groups (Y mesh LSC + RA LSC v. Dual mesh LSC + RA LSC). With a continuous outcome and two categorical independent factors, a two-way

analysis of variance will be used to evaluate differences between the groups. The results will be presented in a standard ANOVA table, which should be sufficient to determine if differences exist. A linear regression will be done to demonstrate actual changes in surgical time attributed to each variable. We will control for LSC ASC and RA LSC ASC by performing a logistic regression. Cost utility analysis will be used to compare the differential mean operating room costs with incremental cost effectiveness ratios (ICERs) calculated as appropriate.

Summary of tasks for study:

	Preop	OR	6 wk postop	6 mo f/u	12 mo f/u	24 mo f/u
Informed consent	X					
Demographic data	X					
Randomization	X					
PFDI-20	X		X	X	X	X
POP-Q	X			X	X[1]	X[1]
OR data collection sheet		X				
Review of d/c summary, chart, postop Hct, complications (ER visits, etc)			X	X	X	X

1. **POP-Q – Optional but encouraged at 12 and 24 months.**

References:

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