PROTOCOL TITLE: MICRO (Minimally Invasive Burch Colposuspension to Reduce Occult Stress Incontinence)
Clinical trial registration: NCT03841513

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VERSION NUMBER: 5 **VERSION DATE:** 10/6/20

STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	N/A
IND / IDE / HDE #	
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	50
Funding Source	Northwestern Friends of Prentice Grants Initiative
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent

	☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☐ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☐ Yes ☒ No

OBJECTIVES:

Purpose: The purpose of this study is to examine surgical outcomes when prophylactic minimally-invasive laparoscopic (including robotic) Burch colposuspension is performed at the time of laparoscopic sacrocolpopexy.

Hypothesis: Stress-continent women undergoing laparoscopic sacrocolpopexy will have higher rates of occult stress urinary incontinence without the addition of the laparoscopic Burch colposuspension.

Specific Goals and Objectives:

Primary Objective:

1. To determine if addition of laparoscopic Burch colposuspension to planned laparoscopic sacrocolpopexy improves rates of stress urinary incontinence (SUI) in stress-continent women undergoing sacrocolpopexy for pelvic organ prolapse (POP). SUI will be defined by a composite outcome of: positive retro-fill cough stress test at 300mL, answer of "yes" to question #17 of Pelvic Floor Distress Inventory 20 (PFDI-20), or any treatment for SUI.

Secondary Objectives:

1. To compare short-term complications in women with and without addition of laparoscopic Burch to sacrocolpopexy.
2. To compare urinary symptoms (urgency urinary incontinence, urgency/frequency, UTI, and retention) in women with and without addition of laparoscopic Burch to sacrocolpopexy utilizing Pelvic Floor Distress Inventory 20 (PFDI-20).
3. To compare bowel symptoms in women with and without addition of laparoscopic Burch to sacrocolpopexy utilizing Pelvic Floor Distress Inventory 20 (PFDI-20).
4. To compare sexual function in women with and without addition of laparoscopic Burch to sacrocolpopexy, utilizing Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire 12 (PISQ-12).

BACKGROUND:

In the United States it is estimated that 13% of women will undergo surgery for POP by age 80. [1] In patients without symptoms of stress urinary incontinence (SUI), surgical correction of pelvic organ prolapse (POP) by itself can result in postoperative occult SUI. Two multicenter randomized trials of stress-continent women undergoing vaginal or open prolapse surgery showed lower rates of postoperative SUI if patients undergo concomitant anti-incontinence procedures. [2, 3] However, adverse outcomes vary based on the type of anti-incontinence procedure (open Burch colposuspension or retropubic midurethral sling) and route of surgery (open or vaginal), and therefore the preferred approach to address occult SUI is unknown.

Sacrocolpopexy is the gold standard surgical repair of pelvic organ prolapse of the apical compartment. The Burch colposuspension is a retropubic procedure in which the periurethral tissue of the anterior vagina is affixed to Cooper's ligament on either side using permanent suture bridges. In the Colpopexy and Urinary Reduction Efforts (CARE) trial [2] patients without preoperative symptoms of SUI were randomized to receive or not to receive concomitant prophylactic Burch colposuspension at the time of abdominal sacrocolpopexy. At three months, the subjects who underwent the Burch procedure were found to have lower rates of SUI after surgery (33.6%) compared to the control group (57.4%). Furthermore, of patients who tested negative for SUI on preoperative urodynamic testing, 22.9 % of those who underwent the Burch procedure had SUI compared to 47.9% in the control group. Burch colposuspension did not increase the rate of urinary retention, urge incontinence, urinary urgency, urinary tract infection, intra or post-operative complications. The data in this trial supported the placement of prophylactic Burch colposuspension at the time of abdominal sacrocolpopexy.

Over the last decade, there has been a shift away from open routes of surgical access secondary to decreased morbidity and quicker recovery associated with minimally invasive procedures. [4-7] As a result, open abdominal sacrocolpopexy with Burch colposuspension has fallen out of favor, and minimally invasive laparoscopic sacrocolpopexy is performed with greater frequency. Additionally, midurethral slings (MUS) have become the gold standard surgical procedure for the treatment of SUI and are performed more frequently than Burch colposuspension at the time of prolapse surgery. The Outcomes Following Vaginal Prolapse Repair and Midurethral Sling (OPUS) study [3] examined the placement of prophylactic MUS at the time of vaginal prolapse surgery. Patients with MUS had lower rates of SUI than control group at 3 months (23.6% vs 49.4%) and at 12 months (27.3% vs 43%). However, unlike the CARE trial, patients with concomitant anti-incontinence procedure had higher rates of adverse events including bladder perforation (6.7% vs 0%), UTI (31.0% vs 18.3%), major bleeding (3.1% vs 0%), and incomplete bladder emptying at 6 weeks (3.7% vs 0%). In addition, MUS carries the risk of mesh erosion into the vagina or urinary tract.

By studying the addition of laparoscopic (including robotic) Burch colposuspension to laparoscopic sacrocolpopexy, we anticipate optimizing surgical outcomes and minimizing complications for patients.

REFERENCES:

1. Wu, J.M., et al., *Lifetime risk of stress urinary incontinence or pelvic organ prolapse surgery.* Obstet Gynecol, 2014. **123**(6): p. 1201-6.
2. Brubaker, L., et al., *Abdominal sacrocolpopexy with Burch colposuspension to reduce urinary stress incontinence.* N Engl J Med, 2006. **354**(15): p. 1557-66.
3. Wei, J.T., et al., *A midurethral sling to reduce incontinence after vaginal prolapse repair.* N Engl J Med, 2012. **366**(25): p. 2358-67.
4. Geller, E.J., et al., *Short-term outcomes of robotic sacrocolpopexy compared with abdominal sacrocolpopexy.* Obstet Gynecol, 2008. **112**(6): p. 1201-6.
5. Hsiao, K.C., et al., *Comparison of laparoscopic and abdominal sacrocolpopexy for the treatment of vaginal vault prolapse.* J Endourol, 2007. **21**(8): p. 926-30.
6. Klauschie, J.L., et al., *A comparison of laparoscopic and abdominal sacral colpopexy: objective outcome and perioperative differences.* Int Urogynecol J Pelvic Floor Dysfunct, 2009. **20**(3): p. 273-9.
7. Paraiso, M.F., et al., *Laparoscopic and abdominal sacral colpopexies: a comparative cohort study.* Am J Obstet Gynecol, 2005. **192**(5): p. 1752-8.

STUDY ENDPOINTS:

1. The primary study endpoint is to compare rates of SUI at 3 month post-operatively in patients who undergo laparoscopic sacrocolpopexy with and without Burch colposuspension. SUI will be defined by a composite outcome of: positive retro-fill cough stress test at 300mL, answer of “yes” to question #17 of Pelvic Floor Distress Inventory 20 (PFDI-20), or any treatment for SUI.

2. The secondary study endpoint is to compare complications, urinary symptoms, bowel symptoms, and sexual function in women with and without addition of laparoscopic Burch to sacrocolpopexy using the Pelvic Floor Distress Inventory 20 (PFDI-20) and Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire 12 (PISQ-12).

PROCEDURES INVOLVED:

Randomization: Enrolled subjects will be assigned to one of two treatment groups with equal probability: laparoscopic Burch colposuspension or no incontinence procedure. A randomly permuted blocked randomization schema will be generated and maintained by a statistician not otherwise involved in the study. Treatment allocation will be performed in the operating room on the day of surgery via email. Electronic records of when the email is opened will be tracked to ensure study allocation is not done prior to the day of surgery. Participants and study

coordinators will be blinded to study intervention until 3-month data are collected.

Blinding: The study surgeons will provide clinical care to study participants, and therefore blinding the surgeon to treatment allocation is not feasible. However, we intend that all outcomes assessors and participants will be blinded to treatment allocation until 3-months outcomes are collected.

To maintain blinding in the dictated operative note under the "Procedure" heading, the procedure will be listed as "laparoscopic or robotic-assisted laparoscopic sacrocolpopexy per study protocol"; however, details of the approach including performance of Burch colposuspension will be described in the text of the operative note when applicable. Similarly, all notes in the electronic medical record and the surgical consent will be listed as "laparoscopic or robotic-assisted laparoscopic sacrocolpopexy per study protocol". A flag will be placed in the inpatient and outpatient electronic medical record indicating that the patient is enrolled in the study so her study procedure is not revealed to her. If unblinding does occur, the study coordinator will complete a protocol deviation form.

Study Intervention: On the day of surgery patients will undergo standard laparoscopic or robotic sacrocolpopexy. The patients randomized to receive the Burch colposuspension will undergo this procedure as described below:

The retropubic space is exposed by dissecting the bladder and urethra posteriorly off of the pubic bone. Next, the area lateral to the urethra is cleared until anterior vaginal wall is identified. Non-absorbable monofilament suture (such as polytetrafluoroethylene or Gore-tex) is placed through Cooper's ligament, followed by a full thickness bite (excluding epithelium) of the anterior vaginal wall parallel to the urethra, and then back up through Cooper's ligament, so that the suture ends can be tied above the ligament. The location of each suture is as follows: a distal suture is placed approximately 2cm lateral to the proximal third of the urethra, and a proximal suture is placed 2cm lateral to the bladder wall at the level of the urethrovesical junction. This is repeated on the contralateral side for a total of 4 sutures. The sutures are tied down to form a suture bridge between the anterior vagina and Cooper's ligament, resulting in the gentle elevation of the anterior vaginal wall. Finally, the retropubic space is re-peritonealized using delayed absorbable suture. (Walters and Karram, Urogynecology and Reconstructive Pelvic Surgery 2015).

As per standard operative protocol, cystourethroscopy will be performed on every patient at the conclusion of the surgery to evaluate for any bladder, urethral, or ureteral injury. No sham procedure will be performed in patients in the control group.

Participant Clinical Assessment: Participants will undergo standardized assessments at baseline and 3-months after surgery including demographics, past medical and surgical history, prolapse assessment using prolapse quantification system (POP-Q), retrofill cough stress test at 300mL, and completion of validated pelvic floor and sexual function symptom questionnaires including

Pelvic Floor Distress Inventory 20 (PFDI-20) and Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire 12 (PISQ-12).

Safety Assessment and Follow up: Study participants will undergo established safety assessment and follow up protocols for post-operative patients. Participants will undergo standardized retrofill voiding trial in postoperative care unit (PACU) prior to hospital discharge to assess for voiding dysfunction. Patients with voiding dysfunction (defined as voiding less than 150mL following instillation of 300mL of sterile water) will be instructed to perform clean intermittent straight catheterization (CISC) or have indwelling Foley catheter placed based on patient preference and ability. An after-hours answering service is available for urgent patient questions and concerns. Participants will receive a standard follow-up phone call by office staff on post-operative day #1. Participants will have standard postoperative follow up appointments at 2 weeks and 3 months to assess for postoperative complications (urinary tract infection, voiding dysfunction, surgical site infection, mesh erosion).

No audio/video recordings will be utilized for this study.

	Pre-Op Visit	PACU	2 Week Post-Op ± 2 weeks	3 Month Post-Op ± 4 weeks
Subject Recruitment/Consenting	X			
Collection of Clinical/Demographic Information	X			
POPQ Measurements	X		X	X
PFDI-20	X		X	X
PISQ-12	X		X	X
Empty Supine Stress Test	X			
Surgical Procedure Form		X		
Retrofill Voiding Trial		X		
Assessment of Adverse Events Form			X	X
Retrofill Cough Stress Test at 300 mL				X

DATA AND SPECIMEN BANKING

Data will be collected and stored at Northwestern Medicine. All study data will be recorded on Data Collection Forms by a research coordinator or study personnel and securely maintained in a locked cabinet that only study personnel have access to. Data will be entered by a research coordinator at Northwestern into a REDCap database that will be stored on a secure sever. Only

study staff will have passwords to access the project data on REDCap. All users of REDCap need an institutional username and password to log in and to enter data. Research personnel, including study staff as well as study doctors will be able to collect and have access to subject data.

After all data is collected, it will be downloaded from REDCap to Excel and SPSS and analyzed on Northwestern servers only and on computers that are Northwestern property and password protected by Northwestern.

SHARING RESULTS WITH PARTICIPANTS

Participants may inquire about the individual measurements of their exam if desired. Patients can be unblinded after their 3 month visit. Study results may be given to patient at the completion of the study.

STUDY TIMELINES

An individual will participate in the study for a maximum of 4 months from the time of enrollment. Participants will be enrolled in the study at their preoperative visit and will be evaluated again in the postoperative recovery room, at the 2 week and 3 month post-operative visits.

We originally anticipated that it would take 24 months to enroll 50 patients however recruitment has taken longer. Adding an additional recruitment site will help us with our efforts. We anticipate recruitment will be completed December 2021 with analysis completed by June 2022.

	Months 1-12	**Months 4-15**	**Months 15-16**
Patient Enrollment	X		
Patient Follow-up Period		X	
Data Analysis			X

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

- Women over age 18
- English or Spanish speaking and reading
- Symptomatic pelvic organ prolapse with any compartment at or beyond the hymen

- Stress-continent, as defined as response of “no” to question 17 of PFDI-20: “Do you usually experience urine leakage related to coughing, sneezing, or laughing?”, as well as a negative empty supine stress test.
- Planning laparoscopic or robotic sacrocolpopexy, with or without hysterectomy
- Have completed childbearing

Exclusion Criteria
- Adults unable to consent
- Pregnant women or patients desiring future pregnancy
- Patients undergoing uterine sparing surgery
- Individuals under age 18
- Prior procedure for stress urinary incontinence
- Prior retropubic surgery

VULNERABLE POPULATIONS

N/A

RECRUITMENT METHODS

This study will recruit patients who present to the Urogynecology Clinic at the Integrated Pelvic Health Program (IPHP), Lake Forest Hospital, and Central DuPage Hospital, at the time of their initial or follow up surgical consult appointment. Specifically, women without symptoms of SUI, defined as a negative answer in response to question #17 in the Pelvic Floor Distress Inventory (PFDI)-20 who are planning to undergo minimally invasive sacrocolpopexy for symptomatic POP at or beyond the hymen will be approached for recruitment. There will be no external advertising.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

Study participants will receive a $100 gift card at the end of the study follow up period.

Participants will be notified of their blinded treatment allocation at the end of the 3 month follow up period. They will be informed, upon request, the findings of the study once all data have been collected and analyzed.

WITHDRAWAL OF PARTICIPANTS

We do not foresee any participants needing to be withdrawn without their consent. Participants who withdraw from the study for any reason will continue to be followed as routine post-surgical patients.

RISKS TO PARTICIPANTS

Potential adverse events from Burch colposuspension include urinary tract infection, cystotomy, ureteral injury, and ureterovaginal fistula formation. In the CARE trial, the rates of adverse events were rare and similar in patients undergoing sacrocolpopexy with and without Burch colposuspension (4.5% and 3%, respectively). Patients randomized to the Burch colposuspension had longer operating room times (20 additional minutes) and increased blood loss (additional 73mL). The clinical impact of these factors is thought to be minimal.

There are no foreseeable psychological, social, legal, or economic risks to participants.

Patients undergoing sacrocolpopexy at our institution undergo concomitant hysterectomy, or have already had a hysterectomy in the past. Patients who desire uterine-sparing prolapse surgery will be excluded from this study. Therefore by design, this study will not pose any risk to an embryo or fetus.

POTENTIAL BENEFITS TO PARTICIPANTS

Our current standard of care for patients undergoing POP repair includes urodynamic testing. Per the study protocol, participants will not have to undergo urodynamic testing, thereby avoiding a potentially uncomfortable diagnostic test.

Potential benefits to participants randomized to receive Burch colposuspension include possible decreased risk of developing occult SUI following prolapse repair and therefore a lower probability of needing subsequent treatment.

DATA MANAGEMENT AND CONFIDENTIALITY

The primary outcome measure is stress incontinence symptoms 3-months after surgery. In CARE, 34% of women randomized to open Burch and 57% of controls had stress urinary incontinence 3-months after surgery. Assuming addition of a minimally invasive Burch colposuspension to minimally invasive sacrocolpopexy will result in similar rates of stress urinary incontinence, a sample size of 42 (21 in each group) would demonstrate that addition of a Burch is superior to no Burch with a superiority margin 15%, 80% power and type 1 error of 5%. Assuming a 15% study dropout rate, a total of 50 patients will be recruited for this study.

Data will be collected at Northwestern Medicine. All study data will be recorded on Data Collection Forms by a research coordinator or other member of the study team and securely maintained in a locked cabinet to which only study personnel have access. Data will be entered by a research coordinator at Northwestern into a REDCap database that will be stored on a secure server. Only study staff will have passwords to access the project data on REDCap. All users of REDCap need an institutional username and password to log in and to enter data. Research personnel, including study staff as well as study doctors, will be able to collect and have access to subject data.

After all data is collected, it will be downloaded from REDCap to Excel and SPSS and analyzed on Northwestern servers only and on computers that are Northwestern property and password protected by Northwestern.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

Adverse events associated with Burch colposuspension in conjunction with sacrocolpopexy will be recorded, and will include events such as post-operative urinary retention requiring catheterization, post-operative urinary tract infection, and persistent urinary urgency.

Subjects will be monitored at each study visit for adverse events. An assessment of adverse events form will be completed and will be recorded into REDCap electronic data capture system. The PI will be notified of any adverse events, which will be resolved with the patient.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

To protect privacy interests, the personal health information collected for research purposes will be collected from the subject's electronic medical record to limit the amount of people they interact with and provide personal information to.

All interviews will be conducted in a private office or examination room to ensure confidentiality. Phone conversations will be conducted from private offices. Any study correspondence with patients will not indicate disease status or focus on the envelope. All physical exams will be conducted in a private examination room. Subjects will be allowed to skip any question on a questionnaire that makes them feel uncomfortable.

The study staff, including investigators and the study coordinator, will have access to the subject's medical record and study documents. All study documents will be kept in a locked cabinet and only those with password required access to EPIC will be able to access the subject's electronic medical record.

COMPENSATION FOR RESEARCH-RELATED INJURY

Subjects in need of medical follow-up will be referred to their provider. There will be no compensation for research-related injury.

ECONOMIC BURDEN TO PARTICIPANTS

There are no economic costs to participants and no additional visits than would be expected of them for routine care.

CONSENT PROCESS

A few days before the patient's scheduled urodynamics appointment, a physician on the study team will call the patient to introduce the study and answer any questions they may have. The physician calling the patient will have a treatment relationship with the patient. This call is done because if the patient decides to participate in the study, they no longer have to undergo urodynamic testing. The research coordinator will email the patient a copy of the consent form after the physician speaks with them and will provide them with the research team's direct phone number in case they would like any more information or questions answered. Emailing the consent form will give the patient an opportunity to read over the entire consent form and consult with family prior to coming in for their urodynamics and pre-op appointment.

At the urodyanmics/pre-op appointment consent will be obtained from the patient by a member of the study team if the patient is ready to make a decision. The person obtaining consent will ensure the subject understands the purpose and procedures of the study. After all the subject's questions have been answered, the subject will be given time to make a decision about enrollment. The original signed written consent form will be kept separately from research data at Northwestern, and a signed copy will be given to the patient. Decisionally-impaired subjects will not be enrolled in our study.

The participants will also be able to take the consent form home from their urodynamics and pre-op appointment to think about whether they would like to participate if they are undecided. Since they will not be coming in for any additional appointments before their scheduled surgery, we would like to have the option of electronic consent in RedCap. This will allow the participant to sign consent electronically and complete their baseline surveys via RedCap prior to surgery. This electronic consent form will not differ than the standard in-person consent form.

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)

To protect privacy interests, the personal health information collected on the research forms for research purposes will be kept in a locked cabinet.

The study staff, including investigators and the study coordinator, will have access to the subject's medical record to confirm inclusion/exclusion criteria. Only those with password required access to EPIC will be able to access the subject's electronic medical record.

All interviews will be conducted in a private office or examination room to ensure confidentiality. Phone conversations will be conducted from private offices. Any study correspondence with participants will not indicate disease status. All physical exams will be conducted in a private examination room. Subjects will be allowed to skip any question on a questionnaire that makes them feel uncomfortable.

NON-ENGLISH SPEAKING PARTICIPANTS

Some prospective participants will be Spanish speaking patients. Translational services will be utilized to translate study documents, including consent forms, from English to Spanish. In addition, several members of the clinic nursing staff are native speakers of Spanish. Unfortunately, study questionnaires are not consistently validated in other languages, and patients who are unable to speak and write in either English or Spanish will not be eligible for the study.

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

The research will be carried out within the Integrated Pelvic Health Program (IPHP) in the division of FPMRS at Northwestern University Feinberg School of Medicine. Our program is a well-funded, interdisciplinary, patient-oriented clinical and translational research program with a long track record of training successful surgeon-scientists. We have interdisciplinary faculty members who are dedicated to research and mentoring, which will help ensure the successful completion of the proposed project.

Due to the high volume of patients that present with pelvic organ prolapse to our clinic, it is feasible that the required number of suitable subjects will be recruited within the estimated window of time. Also, study participants will be treated according to our practice's standard treatment protocol, which includes 2 and 14 week postoperative appointments. No additional appointments will be required to complete study procedures.

Availability of mentors/colleagues: Sarah Collins, MD and Kimberly Kenton, MD, MS will serve as the primary investigators for this research. Dr. Collins is an experienced clinical investigator in the field of urogynecology. Dr. Kenton has over a decade of experience as a funded clinical investigator and a successful research mentor. Our research team meets weekly to ensure collaboration and timely progress of all on-going research. We review new project ideas, study design issues, ethical issues around human subject's research, recruitment and retention in on-going studies, database management and statistical analysis, and dissemination.

Clinic Space: The Women's IPHP is a state of the art, multifaceted clinic spaces designed for interdisciplinary care of women with pelvic floor disorders. Each year we see approximately 1600 new FPMRS patients and engage in over 20 prospective, translation or randomized trials, many of which are multi-center and nationally-funded. There are 3 fully functional sites of the IPHP, and each one offers numerous examination rooms, procedure areas, and on-site physical therapy space. The clinics also house dedicated office space and equipment for our full-time research coordinators.

Office/Computer: Each faculty, fellow, and research coordinator have unlimited access to computers equipped with SPSS Statistical Software located in their own academic offices.

Research coordinators: The Division of FPMRS has two dedicated research coordinators. The coordinators are physically located in the clinic space so that they are available for sample

collection, consent, survey collection and data entry. They are present for every weekly research conference to ensure progress on all research projects.