

## INVESTIGATOR STUDY PLAN - REQUIRED

1) **Title:** The Effect of oral Phenazopyridine on Perioperative voiding After mid-urethral sliNg (EPIPhANy study)

2) **IRB Review History\***

*N/A*

3) **Objectives\***

- a) Primary objective: Evaluate the effect of phenazopyridine (brand name Pyridium) on immediate postoperative voiding function in patients undergoing midurethral slings
- b) Secondary objective: Evaluate percent pain reduction with and without use of oral Pyridium at two hours post-procedure.

4) **Background\***

The midurethral sling (MUS) is a very common, highly successful procedure for the management of stress urinary incontinence due to urethral mobility, with cure rates ranging from 80 to 86%.<sup>1</sup> A common complication of the MUS procedure is short-term postoperative voiding dysfunction. Approximately 20% (7) of patients undergoing MUS are unable to void in the immediate postoperative period and are discharged home with indwelling bladder catheter for 3-5 days.<sup>1, 2</sup> Virtually all patients discharged with a catheter are able to effectively void within 5 days of the procedure and long-term voiding dysfunction is extremely uncommon.

A secondary analysis of a recent study at UMass examining the effect of local anesthetic on postop voiding function showed a potentially dramatic effect of oral phenazopyridine on reducing postoperative voiding dysfunction. During the study, a medication used to dye the urine blue to assess for ureteral injury became briefly unavailable commercially. As a result, we preoperatively gave all patients Pyridium because it has the side effect of dying the urine orange. This allowed us to evaluate the flow from the ureters if needed. This transition occurred in the middle of the study and at the conclusion, we observed that the rate of voiding dysfunction decreased from approximately 28% in those not receiving pyridium to 10% in those receiving pyridium. Because the study was not designed to study this serendipitous finding, we propose to formally assess the validity of this observation.<sup>3</sup> Other than our study, there are no other publications that demonstrate that phenazopyridine may have an effect on postoperative short-term voiding dysfunction. At this time there is no evidence of adverse effect to denying patients phenazopyridine. Because of the nature of our surgical practice, many of the procedures we perform have the risk of ureteral injury and we made a decision to give this medication preoperatively to all of our patients. In the 15 years that the PI has practiced, we have never seen a ureteral injury in a patient undergoing a midurethral sling. The documented risk of injury to the lower urinary

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tract during anti-incontinence surgery is approximately 2.6%, with all of these injuries being to the bladder or urethra and 0 ureteral injuries in 351 cases.<sup>4</sup> There is no place for phenazopyridine in the management or assessment of injuries to the bladder or urethra and many providers at UMass and other institutions in the US do not give phenazopyridine to their patients undergoing a midurethral sling. Phenazopyridine is the only oral medication that is available to evaluate the patency of the ureter after pelvic surgery.

### References:

1. Nilson CG, Rezapour, M, Falconer C (2003) 7 year follow-up of the tension – free vaginal tape (TVT) procedure. Int Urogynecol J Pelvic Floor Dysfunct 14 (Suppl I.): S 35.
2. Nilson CG Kuuva N, Falconer C, Rezapour M, Ulmsten U, (2001) Long term results of the tension-free vaginal tape (TVT) procedure for the vaginal treatment of female stress incontinence. Int Urogynecol J Pelvic Floor Dysfunct 12( Supple. 2): S5-8.
3. Voiding function after Mid-Urethral Slings with and without local anesthetic: Randomized Controlled Trial. UMass IRB H-14197
4. Tulikangas PK, Weber AM, Larive AB, Walters MD. Intraoperative cystoscopy in conjunction with anti-incontinence surgery. Obstet Gynecol. 2000 Jun;95(6 Pt 1):794-6.

### 5) Inclusion and Exclusion Criteria\*

#### Inclusion criteria:

1. Any female subjects scheduled to undergo Mid-Urethral Sling (MUS) through the UMass urogynecology service for incontinence.

#### Exclusion criteria:

1. Planned concurrent prolapse or other procedure besides cystoscopy
2. Using intermittent self catheterization preoperatively
3. Undergoing spinal anesthesia for the procedure
4. Known allergy to phenazopyridine (AKA Pyridium)
5. Renal insufficiency
6. Any condition or situation that in the attending physician's opinion would contra-indicate the use of phenazopyridine
7. Subjects not competent to give consent
8. Prisoners
9. Non-English or non-Spanish speaking patients
10. Age <18
11. Pregnant patients
12. Contraindications to the use of IV methylene blue including
  - a) Patients with known hypersensitivity reactions

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- b) Severe renal insufficiency
- c) Patients with G6PD deficiency

### 6) Study-Wide number of Subjects\*

*N/A not a multicenter study*

### 7) Study-Wide Recruitment Methods\*

*N/A not a multicenter study*

### 8) Study Timelines\*

- Participants will be enrolled in the study for approximately 6 weeks.
- We anticipate 2 years to enroll all the subjects into the study
- Primary analysis will be completed within 6 months after enrollment is completed.

### 9) Study Endpoints\*

- Primary outcome is the rate of voiding dysfunction between the two groups.
- Secondary outcomes include: complications, perioperative pain scores,
- Once 50% of the subjects have completed their procedures, we will perform an interim analysis of the rates of voiding dysfunction. If there is a statistically significant difference ( $p < 0.01$ ) at this interval analysis, we will terminate the study.

### 10) Procedures Involved\*

#### Study design and randomization

This study is a randomized controlled trial. Randomization will be performed using software and a block randomization scheme. Study assignment will be completed using sequentially numbered sealed opaque envelopes. All the research procedures described other than the use or not of phenazopyridine will be applicable to both arms of the study. Subjects will have a 50% chances of getting either phenazopyridine or nothing.

Because pyridium turns the urine orange, it is impossible to blind the patients and researchers to the study assignment. Because there is no known placebo that turns the urine orange, there is no value to using an actual placebo tablet. Subjects will be assigned to either receive pyridium or not receive pyridium preoperatively.

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Screening potential subjects: Investigators will screen potential subjects for contraindications to methylene blue. Prior obtaining the routine surgical consent for the potential subject's surgical procedure, the patient's medical history in the UMass Electronic Medical Record is routinely reviewed. The medical record will be reviewed for a diagnosis of G6PD and if found, the potential subject will be excluded.

Once written consent has been obtained, subject number will be assigned and the appropriate randomization envelope will be opened. The study assignment will not be formally shared with the subject. Those assigned to the "pyridium" arm will have orders written for the standard 200 mg dose of pyridium to be given on arrival to the Surgical Admissions Care Unit (SACU). Those assigned to the "NO pyridium" arm will have their routine preoperative orders written along with an order for "No preoperative pyridium".

Subjects will then follow the routine perioperative care for their procedures with the only study interventions being the gathering of PHI and performing postoperative pain assessments.

PHI will be obtained at the time of the surgical consent with the purpose to evaluate for possible confounders affecting the postoperative bladder function.

### **Surgical procedure:**

The Mid Urethral Sling will be performed in standard fashion based on manufacturer's recommendations and instructions to minimize inter-observer variations. We will perform the procedure according to our usual and customary techniques. The subject will receive the same technique and interventions that a routine patient on the Urogyn service would expect to undergo. There will be no changes to the technique for the purpose of the study.

### **Bladder challenge:**

Patient will undergo voiding trial at same day surgery per our usual and customary protocol. This is the same protocol the subject would undergo as a patient on the Urogyn service. The bladder challenge will be interpreted in our usual manner and the subject managed according to our routine clinical protocols.

### **Postoperative care:**

Subjects will undergo routine postoperative care and followup. Subjects failing their bladder challenge will be seen in the Urogyn clinic according to routine clinical protocols and data concerning their void trials collected. Subjects will undergo routine followup evaluation 6 weeks postoperatively in the order to assess any potential long-term voiding dysfunction. Information on any postoperative complications will be collected

### **Administration of Visual analog scale:**

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- (1) Visual analog scale for assessment of pain will be administered at two time intervals.
  - (a) **VAS #1)** Preoperative VAS will be done by the principal investigator or any of the study assistants. The VAS form will be part of subject's packet.
  - (b) **VAS#2)** VAS will be administered by one of the study investigators 2 to 3 hours after the surgical procedure in the SACU.

### 11) **Data and Specimen Banking\***

N/A

### 12) **Data Management\***

**Power Calculation:** We used data from the recent "*Urine and Me*" study conducted at UMass. A 20% percent difference in subjects passing the bladder challenge was felt to be clinically significant. In order to capture this difference a power calculation was performed via the Wilcoxon signed-rank test. Based on this, to detect a 20% difference with a  $\alpha$ -error = 0.05 and a power ( $1 - \beta$  error) = 0.80, a minimum of 41 subjects per group (82 total) will need to be recruited. Assuming ~ 10% dropout rate (8), we will seek to recruit 90 patients.

**Data analysis:** Continuous measures will be compared using the unpaired Student's t test. Association between outcome measures and graph assignment will be adjusted according to demographic differences using an analysis of covariance. Standard statistical programs (SAS, SPSS) will be used to determine the mean differences between the voided/catheterize and bladder scanner volumes.

### 13) **Provisions to Monitor the Data to Ensure the Safety of Subjects\***

There is minimal risk involved with the denial of pyridium to subjects. Prior to the withdrawal of indigo carmine from the market in 2014, patients did not routinely receive pyridium preoperatively. Currently a minority of surgeons use pyridium in sling procedures with most using nothing. In the event that the ureters need to be assessed for patency, subjects will be given methylene blue to dye the urine. This is the intervention currently used to assess ureters in procedures where ureteral patency is assessed. Thus both groups are receiving care that is considered within the standard of care.

Subjects will be monitored in a similar manner to all of our postoperative patients. There is a chance that pyridium may be beneficial to patients and that denying this medication may result in less desirable outcomes. This study is specifically designed to look at the issue. We plan to perform an interim analysis of the data once 50% of subjects have completed the study and if there is a clear benefit (or harm) from this medication, will terminate the study early and offer the medication to all patients.

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### 14) **Withdrawal of Subjects\***

Subjects are free to withdraw from the study at any time. If subjects withdraw their participation, any data that has already been collected for research purposes will be destroyed or anonymized so that it can no longer be identified with the subject. There should not be additional data collection of demographic information for research purposes at the time a subject withdraws their consent for the study.

### 15) **Risks to Subjects\***

This study poses minimal risk to subjects. Subjects randomized to the pyridium arm will receive pyridium as it is commonly given to patients undergoing reconstructive procedures currently through the Urogyn division at UMass. Subjects denied pyridium will undergo the same procedures and techniques that our patients not in the study will receive.

One risk from the study is the risk associated with denying subjects preoperative pyridium for their procedure. Because pyridium is used to dye the urine for evaluation of the ureters, in the event there is concern for ureteral injury, patients will be given methylene blue to dye the urine. In addition over the last 5 years and over 300 cases at UMass, there have been no cases where there has been concern for ureteral injury at the time of a midurethral sling placement. In patients undergoing gyn procedures where injury to the ureter is suspected, methylene blue is routinely given to evaluate for ureteral patency. Thus the patients in both arms will be receiving care that is considered standard for these procedures.

Investigators will screen potential subjects for contraindications to methylene blue. Prior obtaining the routine surgical consent for the potential subject's surgical procedure, the patient's medical history in the UMass Electronic Medical Record is routinely reviewed. The medical record will be reviewed for a diagnosis of G6PD and if found, the potential subject will be excluded.

There is a risk of unauthorized disclosure of protected health information. The datasheets will be kept in a locked cabinet in a locked office in the administrative offices of the division on Jaquith 2. The data will be entered into a de-identified, password protected file kept on the departmental computer servers.

### 16) **Potential Benefits to Subjects\***

Subjects who receive pyridium may have a lower rate of perioperative voiding dysfunction and a lower rate of perioperative catheterization.

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### 17) **Vulnerable populations**

*N/A*

### 18) **Multi-Site Research\***

*N/A*

### 19) **Community-Based Participatory Research\***

*N/A.*

### 20) **Sharing of Results with Subjects\***

*N/A.*

### 21) **Setting**

Subjects will be identified and recruited at the urogynecology clinic located at UMass Memorial and the urogynecology clinic at Westborough UMass Memorial Health Care. The urogynecology division has two full time designated surgeons (the PI is one of them) and both will be part of the study. In addition one urogynecology fellow will work as a study assistant. All these three members will participate recruiting subjects and obtaining intraoperative and postoperative data.

There will be no composition or involvement of any community advisory board, and this research will not be conducted outside of UMass or its affiliates.

### 22) **Resources Available**

This research will be conducted through the scheduled urogynecology clinic.

Roles of the members of the study:

- Principal investigator. Identifying potential subjects for the study, consenting of subjects, performing surgical procedures, participating in the data analysis, preparing submissions to the IRB, oversight of the conduct of the study and research personnel.
- Study assistants. Identifying potential subjects for the study, consenting of subjects, assisting in the surgical procedures.
- Biostatistician. The OBGYN Department has a designated biostatistician who will help with the data analysis. The biostatistician will not participate in the recruitment of study subjects.

The PI, co-investigator and all study assistants are CITI-trained. All of them are also clinical members of the urogynecology division at UMass Memorial Medical Center Department of Obstetrics and Gynecology.

Before initiation of the research, all study assistants will be instructed on

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the protocol and research procedures at the urogynecology department's scheduled bimonthly research meetings.

### 23) **Prior Approvals**

*N/A*

### 24) **Recruitment Methods**

Subjects will be recruited through the outpatient Urogynecology clinics of the Urogyn faculty. Patients scheduled to undergo a midurethral slings and meeting criteria will be approached for participation when they present for their preoperative evaluation.

Investigators will screen potential subjects for inclusion and exclusion criteria to the study including contraindications to methylene blue. Prior obtaining the routine surgical consent for the potential subject's surgical procedure, the patient's medical history in the UMass Electronic Medical Record is routinely reviewed. The medical record will be reviewed for a diagnosis of G6PD and if found, the potential subject will be excluded.

Potential subjects will be approached by their surgeon at their preoperative visit. Once eligibility has been confirmed, potential subjects will be offered the opportunity to participate in the study. The study will be reviewed in detail and ample opportunity for questions will be given. The opportunity to decline participation will also be given. For women agreeing to participation, informed written consent will be obtained.

### 25) **Local Number of Subjects**

90 subjects will be enrolled in the study.

### 26) **Confidentiality**

Data on participants will be stored under a participant ID number to ensure confidentiality. This data will be stored initially in a locked filing cabinet until it can be transcribed into the redcap database which will be password protected on the protected redcap server. The database will be a de-identified database. Data will be stored for seven years.

**Data security.** De-identified subject data will be stored in locked filing cabinet in the locked office of the PI. A study key will be maintained linking study numbers to subject identifiers. This dataset will be entered in a computer database which will be stored on a firewall protected, password-protected computer of the PI in a locked office. The subject ID and source documents will be stored in a locked cabinet in the PI office. Personal identifiers will be destroyed at the earliest opportunity, no later than completion of the study.



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### 27) **Provisions to Protect the Privacy Interests of Subjects (HIPAA)**

Participants will be asked to sign a HIPAA authorization. The data collected on participants will be stored in a locked filing cabinet in the locked office of the primary investigator. Only the primary investigator and a co-investigators will have access to it. To further ensure confidentiality, all data will be stored under assigned study ID numbers rather than personal identifiers such as name or medical record number.

### 28) **Compensation for Research-Related Injury**

Because this is minimal risk, there will be no compensation for subjects participating in the study. In the unlikely event of research-related injury, no funds have been set aside and the study subject will be responsible for cost of care of any research related injury.

### 29) **Economic Burden to Subjects**

There is no economic burden to the subjects. Both groups are receiving care that is considered within the standard of care and all examinations, interventions and procedures will be occurring regardless of the subject's participation in the study. The pyridium is administered as part of a global fee for the surgical procedure and there is no charge to the patient or her insurance for this medication. Because phenazopyridine is a low cost generic medication, its cost compared to the cost of the surgical procedure is negligible to the medical center.

### 30) **Consent Process**

The PI and study staff will follow the UMMS Investigator Guidance for Informed Consent (HRP-802). Subjects who agree to participate will be consented per SOP at Urogynecology clinic by the attending performing the mid urethral sling procedure. Patients will be given ample time to decide and after written and verbal consent is given they will be told they can withdraw from study at anytime despite consenting for the study. Additionally, subjects will be encouraged to ask additional questions regarding the study and their participation. A copy of the consent will be provided with the principal investigator number. Subjects will be encouraged to call with any additional questions.

#### *Non-English Speaking Subjects*

Spanish speakers will be invited to the study. A Spanish consent translated from the English version will be used (attachment 8). Dr. Duenas and Dr. Sierra, who is a co-investigators, are native Spanish speakers, and

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developed the Spanish versions of the consents and summary (Attachment # 9). Only Dr. Duenas and Dr. Sierra will be recruiting Spanish speaking subjects following the same steps as above employed for English speakers.

### 31) **Process to Document Consent in Writing**

The PI and study staff will follow the UMMS Investigator Guidance for Documentation of Informed Consent (HRP-803)

### 32) **Drugs or Devices**

Phenazopyridine is a lawfully marketed drug in the United States. The medication is IND exempt based on the following categories:

This medication is considered within the standard of care for the assessment of ureters after an urogynecologic procedure, including midurethral slings. The medication will be orally administered and does not involve a route that increases the risk associated with the use of the product.

This investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.

This investigation is not intended to support a significant change in the advertising for the product.