Title: Effect of Preoperative Fiber on Postoperative Bowel Function

NCT number: NCT04882995

Date: 5/3/21

1. TITLE
Effect of preoperative fiber on postoperative bowel function

2. EXTERNAL IRB REVIEW HISTORY*
N/A

3. PRIOR APPROVALS:
None

Conflict of Interest (COI): N/A
Clinical Engineering Department: N/A
Biohazardous Agents: N/A
Radiation*:* N/A

4. OBJECTIVES*
a) Primary objective: To determine if pre-operative fiber intake reduces time to first bowel movement after surgery.

b) Secondary objective: To evaluate if pre-operative fiber intake reduces pain associated with first bowel movement after surgery.

5. BACKGROUND*

Post-operative constipation is a well-known concern among patients undergoing pelvic reconstructive surgery. A retrospective study reviewing all patient-initiated telephone calls in the postoperative period after pelvic reconstructive surgery found the most frequent concern among patients to be constipation (Ramaseshan, 2018). There are various strategies for managing post operative constipation but few of these are evidence-based. Strategies typically involve stool softeners, laxatives, stool bulking agents or a combination of these medications.

The current evidence has focused on postoperative medications to improve time to first bowel movement. A study by Patel et al. (2010) found that senna-docusate decreases time to first bowel movement postoperatively when compared to placebo in patients undergoing pelvic reconstructive surgery. Another study examined the effect of a standardized post-operative bowel regimen of over-the-counter medications including docusate, Miralax, fiber wafers and Bisacodyl suppositories and found minimal differences between the combination of medications compared to docusate alone (McNanley, 2012).

There has been an increased attention placed on fiber-containing regimens for perioperative bowel management. It is well-documented that the Western diet is low in fiber and most adult women do not meet the recommended consumption of 25g of fiber per day. Moreover, women with pelvic organ prolapse are at higher risk for constipation than controls. One study suggested that this increased risk could partially be explained by lower intake of dietary insoluble fiber in women with prolapse when compared to controls (Arya et al., 2005).

An alternative approach to postoperative constipation involves consideration of the preoperative period. There is an increasing interest in preoperative optimization and preparation for surgery. There is limited information regarding the effect of preoperative therapies and their effect on postoperative constipation. One study examined the effect of pre-operative mechanical bowel preparation on postoperative return to bowel function and found no difference between the intervention and control group (Ballard et al., 2015). However, mechanical bowel preparation is no longer recommended prior to benign gynecologic surgery. Thus far, there have been no studies examining the use of pre-operative fiber supplementation prior to pelvic reconstructive surgery to improve time to first bowel movement after surgery and pain associated with first bowel movement. Fiber may be of benefit as it appears to have a regulating effect on bowel movements.

References:

1. Ramaseshan AS, LaSala C, O'Sullivan DM, Steinberg AC. Patient-initiated telephone calls in the postoperative period after female pelvic reconstructive surgery. Female Pelvic Med Reconstr Surg. 2018:21.
2. Patel M, Schimpf MF, O'Sullivan DM, LaSala CA. The use of senna with docusate for postoperative constipation after pelvic reconstructive surgery: a randomized double-blind placebo controlled trial. Am J Obstet Gynecol. 2010;202(5):479e1-5.
3. McNanley A, Pervich M, Flantz C, Duecy E, Flynn MK, Buchsbaum G. Bowel function after minimally invasive urogynecologic surgery: a prospective randomized controlled trial. Female Pelvic Med Reconstr Surg. 2012;18:882-85.
4. Arya LA, Novi JM, Shaunk A, Morgan MA, Bradley CS. Pelvic organ prolapse, constipation, and dietary fiber intake in women: a case-control study. Am J Obstet Gynecol. 2005;192(5):1687-91.
5. Ballard A, Parker-Autry C, Lin CP, Markland AD, Ellington DR, Richter HE. Postoperative bowel function, symptoms, and habits in women after vaginal reconstructive surgery. Int Urogynecol J. 2015;26(6):817-821.

6. INCLUSION AND EXCLUSION CRITERIA*

Inclusion criteria:

- Women undergoing prolapse repair with or without hysterectomy on the UMass urogynecology service

Exclusion criteria:

- Unable to provide consent
- Under 18 years of age
- Pregnant women
- Prisoners
- As our validated questionnaires are only available in English, we are unable to offer study participation to Non-English speaking subjects
- Because these conditions intrinsically affect bowel function, women with the following

will be excluded: history of inflammatory bowel disease, colorectal cancer, rectovaginal fistula, sigmoid resection or rectal surgery
- Because the use of motility agents can affect bowel function and stool transit, somen using motility agents such as linaclotide will be excluded.
- Concurrent bowel surgery due to potential effect on the surgical field
- Concurrent anal sphincteroplasty due to potential effect on the surgical field - Insulin-dependent diabetes mellitus with known gastroparesis as this would affect transit of fiber supplement
- Patients with a history of phenylketonuria as the psyllium fiber supplement we will be using contains phenylalanine
- History of placement of sacral neuromodulating device for indication of fecal incontinence, as this would affect bowel function

7. STUDY-WIDE NUMBER OF SUBJECTS*
N/A

8. STUDY-WIDE RECRUITMENT METHODS*
N/A

9. STUDY TIMELINES*
Subjects will be enrolled from one week before their surgery until 6 weeks after surgery.

Our urogynecology department had approximately 90 postoperative admissions over 12 months (from October 2017 to October 2018). Given this trend, we anticipate approximately 20-24 months to recruit 84 patients.

Primary analysis will be completed within 6 months after enrollment is completed.

10. STUDY ENDPOINTS*

The primary outcome is the time to first bowel movement among those who receive preoperative fiber supplementation and those who do not.

The secondary outcome is pain associated with first bowel movement.

We also plan to perform an interval analysis after 50% of subjects have completed their surgery to evaluate postoperative bowel function. If a statistically significant difference ($p<0.01$) is found on this analysis, we will terminate the study.

11. PROCEDURES INVOLVED*

Study design and randomization

This study is a randomized trial. We were unable to find a suitable placebo that had the same properties as the psyllium fiber supplementation, and thus we will compare psyllium fiber supplementation to our standard of care, which is no bowel regimen before surgery. Both groups will receive the routine postoperative bowel regimen offered to all patients on the urogynecology service.

Subjects will be screened for eligibility using inclusion and exclusion criteria in our urogynecology clinic after prolapse surgery has been scheduled. Once a patient provides informed consent for the surgical procedure, she will be invited to participate in this study. Once the subject has consented to participate in the study, baseline data will be gathered. Study assignment will be revealed using sequentially numbered sealed opaque envelopes. Randomization will be performed using software and a block randomization scheme to yield a 50% chance of receiving the preoperative fiber supplementation. Those assigned to the intervention group will receive a 7-day supply of fiber supplementation to be taken before surgery. The fiber will be procured, distributed and managed by the investigational drug pharmacy.

Neither the patient nor the provider will be blinded to the allocation of groups. However, our statistician will be blinded to allocation for the data analysis

Psyllium fiber is a commonly used and naturally occurring dietary supplement that is FDA-approved. It is available over-the-counter.

Surgery:

On the day of surgery, we will collect information from the patient about their last bowel movement as well as if they were able to adhere to the fiber regimen, had they been allocated to that group. Prolapse surgery will be performed in the usual manner. There will be no changes to the surgical technique for the purposes of the study.

Subjects will receive routine perioperative and postoperative care for their scheduled surgery. The study intervention will require postoperative data collection including the gathering of PHI, a 5-day bowel diary and recording of post-operative medications.

Postoperative care:

Subjects will undergo routine postoperative care as inpatients and outpatients and have routine follow-up, including a postoperative evaluation at 2 and 6 weeks. Information on any postoperative complications will also be collected, such as severe constipation, infection, urinary tract infection. During our routine 1 week follow up phone call that all patients get, data regarding the primary outcome will be collected. At their 2 week postoperative visit, they will be asked to fill out a validated questionnaire regarding bowel function.

Administration of bowel function-related surveys:

1. Validated questionnaires related to bowel function and pain scores will be administered at two time points:
   (a) At the patient's preoperative visit
   (b) At their routine 2 week postoperative visit, they will submit their 5-day bowel diary. The primary outcome measures will also be gathered via telephone call to occur 1 week after surgery. At this visit, they will also complete a validated questionnaire regarding bowel function.

12. DATA AND SPECIMEN BANKING*

N/A

13. Data Analysis and Management*

Previous studies have found that the average time to first bowel movement ranges between 64 hours – 81 hours[2-5]. Our quality data finds time to first bowel movement averaging approximately 72 hours. Most studies have targeted a 24 hour decrease in time to first bowel movement. We plan to target a similar difference as we feel this is a clinically significant difference in the patient's postoperative recovery period. Using a Pearson chi-squared test with a significance level of 5% and power of 80%, this yields 35 patients per arm (70 patients total). Assuming a 20% drop-out rate, we seek to recruit 84 patients.

Continuous measures will be compared using the Student's t-test. Standard statistical programs (SAS, SPSS, and STATA) will be used to perform these tests.

14. PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS*

Psyllium fiber is a natural-occurring dietary supplement that is available over the counter and is commonly used across millions of individuals in the United States. It comes in insoluble and soluble forms, both of which are important for a balanced diet. We plan to use psyllium in a powdered form, which contains 70% soluble fiber and 30% insoluble fiber. The normal recommended dose for fiber in the form of powdered psyllium is 1 teaspoon up to three times daily. We plan to prescribe 1 teaspoon twice daily in the form of powdered, pre-measured packets that are to be mixed with 8 oz of water or other cool liquid. We will obtain the psyllium fiber through wholesale distribution that has been determined by the investigational drug pharmacy. Receipt, storage, preparation, accountability, dispensing and return/destruction of all study drug will be performed by the Investigational Drug Service (IDS) at the Memorial Campus Inpatient Pharmacy. The Investigational pharmacy has been contacted regarding this study and has received the study protocol and package insert.

The IDS will verify that study drugs supplies are received intact, at the appropriate temperatures, and in the correct amounts from the study drug supplier.

Study drug will be dispensed only by prescription. Research staff will transfer the prepared study medication from the pharmacy to the Urogynecology clinic on West 4th floor of UMass Memorial to give to the subject. The study drug will not be used for reasons other than that described in the protocol. Attached to this protocol is an informational sheet regarding fiber supplementation.

Psyllium fiber supplement is generally well tolerated. It can cause bloating and abdominal discomfort. Subjects will be advised to stop the fiber if they develop symptoms such as abdominal pain, nausea or vomiting. All subjects will have access to our office and an on-call physician should any medication side effects or adverse reactions develop.

If any adverse event were to arise, they would be evaluated by the on-call physician.

We will do an interval analysis of the primary outcome once 50% of subjects have completed the

study. If a statistically significant difference ($p<0.01$) is found in favor of psyllium fiber supplementation, we will terminate the study and offer preoperative psyllium fiber supplementation to all our patients.

15. WITHDRAWAL OF SUBJECTS WITHOUT THEIR CONSENT*

We do not anticipate a situation where a subject would have to be removed from the study.

16. RISKS TO SUBJECTS*

Psyllium fiber is an over-the-counter dietary supplement that is widely available and used by millions of individuals across the country. We believe this study poses minimal risk to subjects. The risks associated with fiber supplementation include abdominal cramping, bloating, and change in bowel habits. Both groups will otherwise receive the routine postoperative care regularly given to our patients.

There is no economic risk to the patient, as we will provide the study medication.

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.

17. POTENTIAL <u>DIRECT</u> BENEFITS TO SUBJECTS*

Subjects who receive the preoperative fiber supplementation may have a decreased time to first bowel movement with less pain associated with first bowel movement.

18. VULNERABLE POPULATIONS*

N/A. No known vulnerable populations are routinely offered these procedures as these conditions are typically seen in women over the age of 40. Prolapse is rarely seen in patients younger than 40 and we have never seen it in a patient under the age of 18. We have never performed surgery on pediatric or pregnant populations. Our clinic does not provide services to incarcerated patients.

19. MULTI-SITE RESEARCH*

N/A

20. COMMUNITY-BASED PARTICIPATORY RESEARCH*

N/A

21. SHARING OF RESEARCH RESULTS WITH SUBJECTS*

Subjects will not be notified of the overall cohort's experience with fiber supplementation.

22. SETTING

Subjects will be identified and recruited in the urogynecology clinic at UMass Memorial on West 4th floor at the time of their pre-operative visit. At this visit, the patients will be consented, and they will also fill out the pre-operative questionnaire. At this time, they will also be randomized

to standard of care versus intervention. The urogynecology division has two full-time designated surgeons (including the PI) and both will participate in the study. In addition, the department fellows and nurse practitioner will work as co-PI and study assistants. This comprises the team who will recruit subjects and obtain intraoperative and postoperative study data.

Data entry and analysis will be performed in the administrative offices of the division on Jaquith 2 in UMass Memorial.

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

23. RESOURCES AVAILABLE

The research team will be comprised of the following: principal investigator, co-principal investigator, study assistants and our department biostatistician. The roles and qualifications of the team members include:

- Principal investigator: is the division director of the urogynecology department and has overseen numerous research studies within the department. He will assist in identifying potential subjects for the study, consenting of subjects, performing surgical procedures, participating in data analysis, preparing submissions to the IRB, oversight of the conduct of the study and research personnel.

- Co-PI: is a first year urogynecology fellow in the department. Fellowship requirements include 12 months devoted to research over 3 years. Assist in identifying potential subjects for the study, consenting of subjects, assisting in surgical procedures, participating in data collection and analysis, preparing submissions to the IRB.

- Study assistants: Consist of fellows within the department, who have participated in other research studies under the direct faculty supervision of the PI and attending physicians in the urogynecology division. They will assist in identifying potential subjects for the study, consent subjects, and assist in the surgical procedures. Our nurse practitioner will assist with data collection in the postoperative period.

- Biostatistician: Our departmental biostatistician has worked with the urogynecology division on several research studies and will help with data analysis.

The PI, co-PI, and 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 the study protocol and research procedures at the urogynecology department's scheduled bimonthly research meetings.

24. LOCAL RECRUITMENT METHODS

Our power calculation, as detailed previously in question 13, requires 70 total subjects (35 per

arm). Assuming a 20% drop-out rate, we seek to recruit 84 patients. Our urogynecology department had approximately 90 postoperative admissions over 12 months (from October 2017
to October 2018). Given this trend, we anticipate approximately 20-24 months to recruit 84 subjects for the study.

All subjects will be identified and recruited through the urogynecology clinic, at the clinic site previously mentioned in question 22, after prolapse surgery has been scheduled. Our two full time surgeons (including the PI) will both participate in the study, as well as the department fellows—therefore, this yields access to every surgical urogynecology patient. The study team will screen potential subjects using inclusion and exclusion criteria at their preoperative visit, since this routinely includes a review of the patient's medical history. No identifiers will be recorded during screening. Once eligibility has been determined, potential subjects will be offered to participate in the study by their surgeon only after surgical consent has been discussed and obtained for the patient's surgery. Clinical staff will not be involved in the recruitment process. The study will be reviewed in detail and ample opportunity for questions will be given. The opportunity to decline participation will also be given, and no information on these patients will be recorded for this study. An un-identified tally will be recorded counting screened patients who were "ineligible" or "declined". For women agreeing to participation, informed written consent will be obtained.

There will be no payment to subjects in the study.

25. LOCAL NUMBER OF SUBJECTS

We seek to enroll 84 subjects in the study.

26. CONFIDENTIALITY

Data on subjects will be stored under a study participant ID number to ensure confidentiality. This data will be stored initially as a hard copy in a locked closet in a locked office until the scheduled surgery occurs and perioperative data is collected. Study data will be collected only under the study participant ID number, and later transcribed on a monthly basis into a de-identified Redcap database by the study assistants. This database is password protected on the secure Redcap server. At that point, completed study charts will be stored in the locked closet. Only the PI and study assistants have access to this key. The document that links the study participant ID number to patient identifiers (medical record number) will be stored in a separate locked filing cabinet in a different departmental locked office. This will also be transcribed to a secure Redcap server. Once the study is published, the subject key will be disposed of via a HIPAA compliant bin, thus anonymizing data. Perioperative study data will be stored for seven years before it is fully deleted from the secure Redcap database with the assistance of the IT department.

27. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

Participants will provide authorization to access their medical records.

There are no study procedures being performed, the intervention is a study medication that is a naturally occurring dietary supplement. The results from their bowel function-related questionnaires will be stored in a deidentified data base.

28. Compensation for Research-Related Injury

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

29. Economic Burden to Subjects

There is no economic burden to the subjects. Both randomized groups will receive our standard of care and all necessary examinations, interventions, and procedures will continue regardless of the subject's participation in the study. We will obtain the study drug and distribute it so there is no additional cost to the subjects.

30. Consent Process

The PI and study staff will follow the UMMS Investigator Guidance for Informed Consent (HRP-802). The consent process will be reviewed at our monthly research meeting prior to study recruitment, and all recruiting study staff are CITI trained. Subjects who agree to participate will be consented at our Urogynecology clinic by the one of their surgeons. Patients will be given ample time to decide if they wish to partake in the study, since the preoperative clinic visit occurs several days before the surgery. Additionally, subjects will be encouraged to ask additional questions regarding the study and they will be informed that they may withdraw from the study at anytime despite their initial consent. A copy of the consent will be provided to the patient, along with the principal investigator number. Subjects will be encouraged to call with any additional questions.

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) to document consent. The consent process will be reviewed at our monthly research meeting prior to study recruitment.

32. Drugs or Devices

The study medication, fiber, is a routine supplement prescribed to our patients in the outpatient setting. It will be ordered by physicians and self-administered by the subjects.

Fiber is a lawfully marketed supplement in the United States. The study medication is IND exempt based on the following:

This medication is considered within the standard of care for the management of constipation and maintaining regular bowel function. The medication will be orally

prescribed 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.