Title: Optimal timing of a second post-operative voiding trial in women with incomplete bladder emptying after vaginal reconstructive surgery: A randomized trial

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Principal Investigator, Co-investigator(s): Jeffrey Schachar, Andre Plair, Whitney Smith, Candace Parker-Autry, Catherine Matthews, Gopal Badlani

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Background, Rationale and Context

Postoperative voiding trials (VT) are performed after reconstructive pelvic surgery due to the heightened risk of transient urinary retention. Studies have reported rates of post-operative urinary retention following surgery for vaginal prolapse ranging from 6-29%, higher than after vaginal hysterectomy for non-prolapse indications. Patients who are unable to successfully void after surgery may be discharged home with an indwelling transurethral catheter for several days until a voiding trial may be repeated in the office. Indwelling catheters are associated with an increased risk in urinary tract infection (UTI), increased discomfort and poor patient satisfaction. It has been shown that duration of catheterization is the most important determinant of developing bacteriuria. Several studies have been performed comparing the length of time a Foley catheter is left in place after a gynecologic surgery. Overall, earlier catheter removal reduces rates of UTI, but has been associated with a higher risk of urinary retention and re-catheterization. VTs aid in the decision-making process as to whether or not a patient is a candidate for early discontinuation of a Foley catheter. With the recent trend toward minimally invasive and outpatient surgeries, patients are frequently discharged home on the day of surgery. In such cases, patients undergo a voiding trial in the recovery room on the same day of surgery, prior to discharge. Patients who are successfully able to empty their bladders may be discharged without a catheter. Those who are unsuccessful have a Foley catheter re-inserted and are discharged with an appointment scheduled for an office voiding trial. The length of time to repeat a voiding trial after an initially failed trial has yet to be studied.

Objectives

Primary Objective

The primary objective of this study is to determine the timing to return to normal bladder function after pelvic floor reconstructive surgery for those patients who failed the initial post-operative VT. To assess this, the rate of failure of repeat VT will be assessed at two post-operative time points.

Secondary Objectives

To evaluate:

- The rates of UTI in the two groups
- Rates of Foley catheter re-insertion after passing a subsequent office void trial
- Patient Satisfaction

Methods and Measures

Design

This study is a randomized controlled trial designed to assess the timing of return to normal bladder function after pelvic floor reconstructive surgery. The primary outcome will be assessed by comparing office VT failure rates between those who return in the early post-operative period (2-4 days) vs the standard time to return for an office VT (1 week). Based on the Hakvoort et al

study and a 95 two-sided significance level and 80% power, this study would require 60 subjects, or 30 per group. Assuming a 10% drop-out rate, 66 total subjects should be enrolled in the study. All patients that meet the appropriate inclusion criteria will be considered for the study. OR schedules will be reviewed and subjects will be assessed for possible eligibility approximately 1-2 weeks prior to surgery. Patients will be counseled about the study either in the office during a surgical planning office visit, over a pre-operative telephone call, or in the pre-operative area just prior to surgery. Consents will be signed in the pre-operative area.

After surgery, the patient will be given a standardized voiding trial as per the usual protocol. If the patient is un-successful in emptying her bladder according to the VT protocol she will be discharged home with an indwelling Foley catheter as per usual protocol. On post-operative day (POD) #1 the patient will be re-assessed for meeting eligibility requirements. Once eligibility is established, the subject will be called on POD#1 and randomized to either the early voiding trial group (EVT) or the late voiding trial group (LVT). Subjects in EVT will be scheduled for a repeat VT on POD#2-4, whereas those in LVT will be scheduled for a repeat VT on or after POD#7. Subjects that are unsuccessful in the repeat VT will have a Foley catheter re-inserted and will return for another VT in 5-7 days. Subjects who fail the third VT from either group will have the Foley catheter replaced and will return for another office VT after waiting an additional 5-7 days or will be started on clean intermittent self-catheterization.

Subjects will be monitored for a 6 week period. During that time the patient will be monitored for voiding and urinary symptoms. Urine will be tested via in-office urinalysis at each office visit (as per usual practice), including pre-operatively, and will be sent for a urine culture per usual practice based upon abnormal urinalysis results (ie. any blood or leukocytes). Urine cultures that grow out a single organism >10,000 CFU will be treated with appropriate antibiotics. In addition, patients will complete quality of life questionnaires at the time of catheter removal and at 6weeks post-operatively.

Setting

The study will take place at two medical centers. Most of the interactions will take place in the office setting, including all pre-operative evaluations, and post-operative follow-up. Surgeries will be performed in the hospital setting.

Subjects selection criteria

- Inclusion Criteria

  Subjects must meet the following inclusion criteria in order to be eligible for the study

  - Female patients age 18 or older
  - Speak English and are capable of giving informed consent
  - Are willing to return to the office for all necessary visits associated with the study
  - Underwent outpatient gynecology pelvic floor surgery for multi-compartment prolapse
  - Failed the voiding trial in the recovery room on POD#0

- Exclusion Criteria

  Subjects must not have any of the following exclusion criteria in order to be eligible for the study

  - Pre-operative urinary retention as defined as PVR > 200ml
  - Prior incontinence surgery
  - Passed the voiding trial in the recovery room

- Require prolonged catheterization due to urethral/bladder abnormality (ie vesicovaginal fistula, urethral diverticulum) or intra-op urethral or bladder injury or for intensive post-operative monitoring
- Patients who take any post-operative antibiotics, other than prophylaxis during catheterization, for reasons other than a UTI as diagnosed and prescribed as part of the study
- Patients who take any supplements to prevent UTIs, including but not limited to D-Mannose, Hiprex, or Ellura
- Have any neurological conditions that may affect bladder function (ie. Multiple sclerosis, spinal cord injuries, etc.)
- Patients with pre-operative narcotic medication use due to chronic pain

- **Sample Size**
  Using OpenEpi.com and the Fleiss statistical method the sample size was calculated for a randomized controlled trial based on the Hakvoort et al. study. With a 95% two-sided significance and an 80% power, this study will need 60 subjects to be adequately powered to test for the primary outcome of differences in Foley catheter re-insertion rates.
  - This is a multi-center study. The coordinating institution is the Cleveland Clinic Florida in Weston, FL. The study has been approved and enrollment is underway at that site. Over 30 patients are already enrolled at that site. Ideally, 20 subjects would be enrolled from Wake Forest Baptist Health in North Carolina.

Interventions and Interactions

- As described above, if the patient does not pass the recovery room VT, a Foley catheter will be inserted for either 2-4 or 7 days depending on the randomization. Prophylactic antibiotics may be used per the surgeon's preference. Length of catheter duration will depend on when the patient is able to pass an outpatient VT.
- As described above, urine cultures will be performed as medically indicated. A single identified organism of 10,000 CFU or greater will be considered a positive culture.
- Pre-operative and post-operative questionnaires will be used to assess patient satisfaction with their voiding/ Foley catheter use.
- Office notes will be reviewed to assess for study eligibility. Background data will be collected for descriptive statistics. Data from urodynamic studies will also be collected as part of the background data. Post-operative notes from the clinic will be reviewed to assess for any complications or adverse events. Surgical and hospital records will be reviewed and various data will be collected to ensure that there was equivalence in the groups for items such as: type of surgery, post-op narcotic use, length of surgery, time to recovery room void trial, etc.
- Length of time spent by each subject on specific study materials will only include the length of time to complete the short questionnaires. The remainder of their care, including surgery, post-operative follow-up, repeat VT are part of the usual post-operative care

			Visit			
	Pre-Study	**Recovery Room**	**V#1 (Repeat VT, either POD 2-4 or 6-7)**	**V#2 (Repeat VT if failed at V#1 Or 2 week post-op visit)**	**V#3 (2 week routine post-op visit or 6 week post-op visit)**	**V#4 (6 week post-op visit, if not completed at V#3)**
Informed Consent	X					

Demographics	X					
Medical History	X		X	X	X	X
Physical Exam	X			X	X	X
Pre-operative Labs	X					
Urodynamic Testing	X					
Voiding Trial		X	X	X		
Patient Questionnaire	X		X	X	X	X
Urine Sample	X		X	X	X	X

Outcome Measure(s)

- Outcomes that will be assessed include: void trial outcomes, UTI rates, urinary retention rates, and patient satisfaction.

Human Subjects Protection

Subject Recruitment Methods

Upcoming surgical schedules will be reviewed 1-2 weeks prior to surgery. Patients will be contacted by a member of the study team to discuss eligibility, review the inclusion/exclusion criteria, and to answer all questions. Consent will be signed prior to surgery. Any subject who wishes to withdraw from the study may do so at any time. When the subject chooses to withdraw, they will be presented with the option to either allow all of the data collected to that point be retained, or if they would like it to be removed.

All data will be kept on secure password protected and encrypted hospital computers and contained within password protected files. Source documents will be kept in a locked drawer on hospital property. Protected health information will be de-identified.

Informed Consent

Signed informed consent will be obtained from each subject. Consent will be obtained by one of the study staff prior to surgery.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed seven years after the conclusion of the study consistent with data validation and study design, producing an anonymous analytical data set. Electronic data will be permanently deleted and source documents will be shredded using the hospital system. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

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Appendix

1. **Consent Form**

Consent to Participate in a Research Study

Study title: Timing of repeat void trial after outpatient multi-compartment prolapse reconstruction

You are being invited to participate in a research study. A research study is designed to answer specific questions about new ways to prevent, detect, and treat disease. Being in a research study is different from being a patient. The purpose of this document is to provide a written summary of the discussion and exchange of research information you had with the research team. It is also for use as a reference during the study.

Please note:

- **You are being asked to participate in a research study**
- **Ask as many questions as needed so you can make an informed decision.**
- **Carefully consider the risks, benefits, and alternatives of the research**
- **Your decision to participate is completely voluntary and will have no effect on the quality of your medical care if you choose not to participate. You can also withdraw from the study at anytime.**

1. INFORMATION ON THE RESEARCH

Why is the research study being done?

You have been scheduled for outpatient pelvic floor surgery. This research is being done to evaluate the timing of repeat voiding trials should the initial voiding trial in the recovery room be failed.

What is involved if you decide to take part in this research study?

If you agree to take part in this study, your surgery will not be effected. During the surgery, all patients have a urinary catheter (Foley) inserted to drain the bladder of urine. In the recovery room, all patients have the catheter removed to see whether they can urinate on their own (voiding trial). If they can't urinate, a Foley is re-inserted.

If you pass the recovery room voiding trial, you will not be randomized to either of the treatment groups. Your data will continue to be collected and followed for research purposes.

If you are unable to urinate in the recovery room, all patients go home with a Foley catheter and return for a repeat voiding trial in the office.

Current practice is to wait 1 week before having the patient return for the office voiding trial. If you agree to partake in this study, you will be randomized on the day after surgery to either returning for an “early repeat voiding trial” in about 2-4 days or returning for the “normal

repeat voiding trial" after 7 days. You will have a 50:50 chance, like the flip of a coin, to be in either group.

If an office repeat voiding trial is failed, patients typically return home with the Foley catheter and schedule another office voiding trial 5-7 days later.

Participants will also be asked to fill out simple questionnaires before and after surgery either by phone or in clinic.

Your information will be collected through the electronic medical record and via the questionnaires. All the results will be recorded in your medical record.

A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this at any time.

2. ALTERNATIVES

What are the alternatives to participation in the research study?

The alternative to participation in this study is to choose to not participate in this study. If you do not participate you will undergo your scheduled surgery and follow up as per the normal routine.

3. RISKS

What are the risks of participating in the research study?

The procedures in this study are considered standard of care. Regardless of participation in this study, if one fails the recovery room voiding trial, they will be discharged home with a Foley catheter and antibiotics and will undergo an office voiding trial about one week after surgery. The only difference is that in this study you may be randomized to the "early" group. If you are in the "early" group, there may be an increased risk of failing the voiding trial and having a catheter longer than you would otherwise. With a longer time with a catheter, there are increased risks of discomfort and bacteriuria (bacteria in the urine). If untreated a bladder infection or kidney infection could result. Given the short interval of your follow up, the risks of the infection going untreated is low.

Confidentiality risks

Data will be password protected and only accessible to the researches in the study medical staff involved in the procedure. The results of the urine tests/cultures will be a part of you medical record and these results can be obtained by those who have access to your medical record.

4. BENEFITS

What are possible benefits of participating in the research?

You may not benefit directly from this research but results from this study may help counsel future patients on the best time to return for an office void trial.

5. COSTS

Are there any costs to you if you participate in this study?

All test and procedures are considered standard of care. You or your insurance company will be responsible for the cost of these test/procedures.

You will be responsible for all co pays and deductibles for the visits.

6. COMPENSATION

Are there any payments to you if you participate in this study?

Participants will not receive any compensation for this study.

7. RESEARCH RELATED INJURY

What will happen if you are injured as a result of taking part in the research?

In the event you are injured as a result of participation in this research, medical care is available to you. The costs of such medical care will be billed to you or your insurance company. There are no plans to provide compensation for lost wages, direct or indirect losses. Wake Forest Baptist Health will not voluntarily provide compensation for research related injury. You are not waiving any legal rights by signing this form. Further information about research related injury is available by contacting the hospital Institutional Review Board.

8. PRIVACY AND CONFIDENTIALITY

What will happen to your information that is collected for this research?

Wake Forest Baptist Health has rules and procedures to protect information about you. Federal and State laws also protect your privacy.

The research team working on the study will collect information about you. This includes your health information, data collected for this research study and personal identifying information including your name, address, date of birth and other identifying information.
Generally, only people on the research team will know your identity and that you are in the research study. However, sometimes other people at the hospital may see or give out your information. These include people who review research studies including the Institutional Review Board and Research Compliance, their staff, lawyers, or other hospital staff.

People outside the hospital may need to see your information for this study. Examples include government groups (such as the Food and Drug Administration), safety monitors, other hospitals in the study and the sponsor of the research and their agents. Wake Forest Baptist Health will do our best to ensure your information is kept confidential and that only the health information which is minimally required to conduct the study is used or disclosed to people outside the hospital; however, people outside the hospital who receive your information may not be covered by this promise.

You do not have to give this permission to use and give out your information; however you will not be able to participate in this research study without providing this permission by signing this consent form. The use and disclosure of your information has no expiration date.

You may cancel your permission to use and disclose your information at any time by notifying the Principal Investigator in writing. If you do cancel your permission to use and disclose your information, your participation in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in the study.

9. QUESTIONS

Who do you contact if you have any questions or problems?

Contact Person: Jeffrey Schachar, MD, JSchacha@wakehealth.edu.
If Dr. Schachar is not available, you may call the office to speak with a physician.

If you have questions as a research subject, you should contact the Institutional Review Board.

10. VOLUNTARY PARTICIPATION

What Are Your Rights As A Participant?

Taking part in this study is voluntary. You will be told of any new, relevant information from the research that may affect your health, welfare, or willingness to continue in this study. You may choose not to take part or may leave the study at any time. Withdrawing from the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to withdraw from the study you should discuss with your study doctor your decision to ensure a safe withdrawal.

11. Signatures

Statement of Participant

I have read and have had verbally explained to me the above information and have had all my questions answered to my satisfaction. I understand that my participation is voluntary and that I may stop my participation in the study at any time. Signing this form does not waive any of my legal rights. I understand that a copy of this consent will be provided to me. By signing below, I agree to take part in this research study.

_____
Printed name of Participant

_____ _____
Participant Signature Date

Statement of Person Conducting Informed Consent Discussion

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

_____
Printed name of person obtaining consent

_____ _____
Signature of person obtaining Date