Randomized controlled trial of vaginal cryotherapy for pelvic floor myofascial pain

Principal Investigator:

Melanie Meister, MD, MSCI

Version Date/Number:

Version 1, 3/15/19

TABLE OF CONTENTS

A Introduction

A1 Study Abstract

Pelvic floor myofascial pain, that is, pain in the internal hip (obturator internus, OI) and pelvic floor (levator ani, LA) muscles, is common in women with chronic pelvic pain. In particular, patients presenting to urogynecologic subspecialists for evaluation of pelvic floor disorder symptoms, are frequently found to have concomitant pelvic floor myofascial pain. (2). Pelvic floor disorder symptoms include bothersome lower urinary tract symptoms (LUTS; urinary urgency, frequency, hesitancy, dysuria, and sensation of incomplete bladder emptying), pelvic organ prolapse, defecatory dysfunction, and pelvic pain.

Treatment options for pelvic floor disorders include medications (typically anticholinergics for overactive bladder symptoms), pessaries (for vaginal prolapse) or surgery (anti-incontinence procedures, vaginal support procedures, etc), but the medications are not fully effective and cause bothersome side effects, and surgery is invasive. Additionally, some patients presenting with pelvic pressure and heaviness, presumed to be vaginal prolapse, are found to have overall good vaginal support on examination. These women are not candidates for pessaries or surgeries as they do not have a defect in vaginal support. *Thus, a new approach to treating pelvic floor disorder symptoms is needed*.

Nearly 25% of women with LUTS are found to have underlying pelvic floor myofascial pain[2], which refers to pain arising in the skeletal muscle and connective tissue of the pelvic floor (levator ani, LA) and internal hip (obturator internus, OI). This number is likely an underestimate because, until recently, no standardized and reproducible pelvic floor myofascial examination protocol existed. In a recent retrospective analysis from our own institution, pelvic floor myofascial pain was significantly correlated with several prolapse *symptoms* as measured on one validated questionnaire, but not with objective prolapse *severity* based on the leading edge [unpublished data] further supporting the role of pelvic floor myofascial pain in pelvic floor disorder symptoms.

Few providers evaluate for pelvic floor myofascial pain, even in patients presenting with pelvic pain[3]. When pelvic floor myofascial pain is identified, women are typically referred for pelvic floor physical therapy (PT)[4-6]. However, pelvic floor PT is performed by PT specialists with advanced training in women's health. Depending on the availability of such specialists (who are generally concentrated in large cities or affiliated with academic medical centers), women could experience a delay in receiving treatment. Additionally, insurance often does not cover PT or only covers it partially. *Thus, we must identify effective options to treat women with pelvic floor myofascial pain and concomitant pelvic floor disorder symptoms aside from PT.*

One treatment that shows promise as an effective means of treating pelvic floor myofascial pain is vaginal cryotherapy. This idea is founded on the following. First,

physicians and women's health PT specialists at our institution routinely prescribe vaginal cryotherapy in addition to pelvic floor PT for treatment of pelvic floor myofascial pain and find, anecdotally, that patients often report improvement in their pelvic floor myofascial pain, even before initiating pelvic floor PT. Second cryotherapy has been used routinely for treatment of musculoskeletal injuries elsewhere in the body, where it functions by decreasing tissue metabolism, blood flow, inflammation, and edema, thereby reducing muscle spasm and pain[7]. Finally, vaginal cryotherapy, referred to as 'condom pops', was reported by focus group participants as an effective treatment option for urologic chronic pelvic pain in a recent MAPP Network trial. [Sutcliffe et al] However, no studies have rigorously tested whether or not vaginal cryotherapy is an effective treatment for pelvic floor myofascial pain.

Our **objective** is to conduct a **randomized controlled trial** to determine the therapeutic effect of vaginal cryotherapy on pain severity and LUTS bother in women with moderate-to-severe pelvic floor myofascial pain. We **hypothesize** that, compared to control (similar device but empty), vaginal cryotherapy will significantly reduce myofascial pain score when used independent of and in conjunction with pelvic floor PT.

A2 Primary Hypothesis

Here we propose a randomized controlled trial to test the overall hypothesis that, compared to control, vaginal cryotherapy will significantly reduce pelvic floor myofascial pain scores when used independent of and in conjunction with pelvic floor PT.

A3 Purpose of the Study Protocol

The purpose of this study protocol is to provide a detailed summary of the study design and methods for study personnel to refer to throughout the course of the study.

B Background

B1 Prior Literature and Studies

The burden of pelvic floor disorder symptoms and inadequacy of treatment approaches: Up to 75% of women experience pelvic floor disorder symptoms like lower urinary tract symptoms (LUTS), which are classified by the International continence Society into storage, voiding, and post-micturition symptoms (1,8). Given that the prevalence of LUTS increases with advancing age (1,9) 18.4% more women are projected to be affected by at least one LUTS in 2018 than 2008 (10). Depending on the presenting symptom, the mainstay of treatment typically involves either medication or surgery. Medications to address overactive bladder symptoms (urinary urgency with or without incontinence, frequency, and nocturia), typically anticholinergics, are associated with a high rate of discontinuation due to bothersome side effects and lack of efficacy (11). Surgical procedures for refractory overactive bladder, including botulinum toxin injections or sacral neuromodulation, are invasive and may not completely address the patient's symptoms. Thus, an effective non-pharmacologic, non-surgical treatment for pelvic floor disorder symptoms like LUTS would likely help thousands of women.

Pelvic floor myofascial pain is common and may underlie pelvic floor disorder

symptoms: Pelvic floor myofascial pain refers to tenderness and trigger points identified within the muscles of the pelvic floor (levator ani, LA) and internal hip (obturator internus, OI) (4). Pelvic floor myofascial pain contributes to 60-85% of chronic pelvic pain and likely underlies a significant proportion of pelvic floor disorder symptoms, including LUTS (2,3,11-14).

Other pelvic floor disorder symptoms, in particular pelvic pressure/heaviness, may indicate underlying pelvic organ prolapse, however, not uncommonly, patients presenting with pelvic pressure/heaviness are found to have normal vaginal support. This suggests that another process may underlie these symptoms other than objective pelvic organ prolapse. Findings from a cross-sectional analysis of new patients evaluated at our tertiary care institution suggest that moderate-to-severe pelvic floor myofascial pain is especially prominent in these patients (14). While pessaries or surgery are the mainstay of therapy for pelvic organ prolapse, patients with symptoms of pelvic pressure/heaviness but normal vaginal support would not be candidates for this treatment. In another regional study, 16% of patients presenting with pelvic floor disorder symptoms, without symptoms of chronic pelvic pain, were found to have myofascial pain in the LA on examination (2). Unfortunately, pelvic floor myofascial pain has received limited attention in the literature and, until recently, a standardized physical examination did not exist (3,29). As a result, few providers routinely evaluate the muscles of the internal hip (OI) and pelvic floor (LA) in the differential diagnosis for patients presenting with chronic pelvic pain or pelvic floor disorder symptoms.

Pelvic floor myofascial pain is treated conservatively: Treatment of pelvic floor myofascial pain typically involves pelvic floor physical therapy (PT), often with treatment of movement impairment disorders and/or myofascial release (4,20). Due to the subspecialty nature of pelvic floor PT, availability is often limited by the number of formally trained providers in a geographic area. As a result, patients may experience a delay between the diagnosis of pelvic floor myofascial pain and the start of pelvic floor PT or not have access to a physical therapist at all. For example, at our institution, patients may experience a delay of up to 4 weeks from diagnosis of pelvic floor myofascial pain to their first pelvic floor PT visit. Furthermore, insurance carriers often impose strict regulation on PT coverage including restricting frequency and number of covered PT visits in a calendar year. Pelvic floor PT is not covered by Medicaid. Thus, even patients with geographic access to pelvic floor PT may be restricted in their ability to use these resources based on their insurance providers.

Evidence for cryotherapy: Cryotherapy, defined as the therapeutic application of a device or substance to the body to reduce temperature (7), has long been used as an adjunct treatment modality for acute and chronic musculoskeletal injuries. Through tissue cooling, cryotherapy decreases tissue metabolism and reduces blood flow to injured tissue, which results in diminished inflammation and edema, ultimately leading to reduced muscle spasm and pain (7). Additionally, neural conductance velocity is slowed, which further contributes to reduction in pain (21). Evidence suggests a beneficial role for cryotherapy in addition to physical therapy in musculoskeletal injuries and myofascial pain elsewhere in the body (22-24), but cryotherapy has not yet been investigated in treatment of pelvic floor myofascial pain. Women's Health Physical Therapists and physicians at our institution routinely recommend vaginal cryotherapy to patients presenting with pelvic floor myofascial pain in addition to pelvic floor PT. Anecdotally, we have seen a significant improvement, and in some cases resolution of, pelvic floor symptoms and myofascial pain when vaginal cryotherapy is used alone or in conjunction

with pelvic floor PT. The pelvic floor muscles are easily accessible through the transvaginal route. Vaginal cryotherapy is an inexpensive, simple therapeutic option that may lead to symptomatic improvement for patients on its own or in conjunction with pelvic floor PT. Given rising healthcare costs and increasing restriction on resources like PT, this represents a treatment option that is more accessible for many women than multiple visits to a specially-trained physical therapist. For women who do have access to pelvic floor PT, incorporating vaginal cryotherapy may enable them to decrease the number of PT visits or provide additional improvement over pelvic floor PT alone.

Preliminary evidence supporting a correlation between pelvic floor myofascial pain and pelvic floor disorder symptoms: To investigate the prevalence of pelvic floor myofascial pain in our population of referral patients and investigate a correlation between pelvic floor myofascial pain and pelvic floor disorder symptoms, we performed a retrospectively-assembled cross-sectional study of all new patients presenting to the FPMRS clinic at Washington University in St. Louis from 1/2014 to 4/2016. All new patients had a pelvic floor myofascial examination performed regardless of their presenting complaint, and pain was recorded on an 11-point verbal pain rating scale (0-10). Of the 833 new patients evaluated during the study period, most (92%) reported bothersome pelvic floor disorder symptoms (13). We found a significant correlation between the presence of pelvic floor myofascial pain on examination and degree of LUTS bother as captured on the UDI-6 and pelvic pressure/heaviness symptoms (15). Most surprisingly, there was no correlation between symptoms of pelvic pressure/heaviness and objective pelvic organ prolapse while there was a significant correlation between pelvic floor myofascial pain and pelvic pressure/heaviness. These results suggest that pelvic floor myofascial pain may be a driver of pelvic floor disorder symptoms in a subset of patients.

Anecdotally, we have seen these patients demonstrate improvement in both their pelvic floor myofascial pain scores as well as pelvic floor disorder symptoms after treatment of their underlying pelvic floor myofascial pain through pelvic floor PT without medications or procedures. We are actively investigating this relationship. We aim to demonstrate that treatment of underlying pelvic floor myofascial pain through focused pelvic floor PT leads to an improvement, not only in pain scores on examination, but also pelvic floor disorder symptom bother. Similarly, by targeting and improving pelvic floor myofascial pain, vaginal cryotherapy could presumably also lead to an improvement in pelvic floor disorder symptom bother.

Development of a standardized myofascial examination protocol. Pelvic floor myofascial pain can be a challenging condition to treat, but more importantly, it is often not diagnosed. Unfortunately, until recently, a consistent and validated examination technique that reliably identifies pelvic floor myofascial pain has not yet been published (29). We recently completed a systematic review that found limited consensus on methods to assess pelvic floor myofascial pain (30). To address this lack of standardization, our team developed a standardized pelvic floor myofascial examination protocol in collaboration with Washington University Women's Health PT faculty. An iterative process was used to standardize the examination. Four physicians performed an initial examination on a simulated patient from the Washington University Standardized Patient Program who provided specific, real-time feedback on location, pressure, and technique of palpation among the examiners. The physicians repeated the examination until consensus was achieved. A force sensor was then used to formally standardize pressure between examiners. This examination protocol has been

implemented in our clinics by all providers, and has been shown to have high correlation between examiners (29).

C Study Objectives

C1 Specific Aims

Specific Aim 1: To determine the effect of vaginal cryotherapy as an immediate treatment modality for patients with pelvic floor myofascial pain.
Hypothesis 1: Vaginal cryotherapy will result in a significant immediate improvement in pelvic floor myofascial pain compared to placebo.

Specific Aim 2: To determine the effect of vaginal cryotherapy as a neoadjuvant treatment modality for patients with pelvic floor myofascial pain awaiting pelvic floor PT.
Hypothesis 2A: Vaginal cryotherapy will result in a significant improvement in pelvic floor myofascial pain compared to placebo.

D Investigational Agent

D1 Clinical Data to Date

Cryotherapy is a well-known and effective adjunct treatment modality for acute and chronic musculoskeletal injuries. Through tissue cooling, cryotherapy decreases tissue metabolism and reduces blood flow to injured tissue, which results in diminished inflammation and edema, ultimately leading to reduced muscle spasm and pain (7). Neural conductance velocity is also slowed, which further contributes to pain reduction (21).

Women's Health Physical therapists and physicians at our institution routinely recommend vaginal cryotherapy to patients presenting with pelvic floor myofascial pain in addition to pelvic floor PT. Anecdotally, we have seen a significant improvement, and in some cases, resolution of pelvic floor symptoms and myofascial pain is used alone or in conjunction with pelvic floor PT. Additionally, patients have self-identified this treatment modality as an effective one for urologic chronic pelvic pain (31). Although this method is commonly employed by physical therapists and patients, there have been no studies on outcomes associated with the use of transvaginal cryotherapy.

D2 Dose Rationale and Risk/Benefits

Due to the lack of prior studies on this therapy, there is little evidence aside from common clinical practice and anecdote to guide our rationale for application frequency. Patients prescribed vaginal cryotherapy by the physicians and physical therapists at our institution are told to keep the cryotherapy tube in the vagina for 10 minutes. Patients are instructed to perform vaginal cryotherapy at least once per day, or more often on an as-needed basis, to achieve pain relief.

It is also possible that some of the anecdotal benefit we have observed is due to myofascial release resulting from massage of the pelvic floor muscles by the tube itself, regardless of the temperature. This study will help elucidate the role of the cryotherapy in treatment of pelvic floor myofascial pain. Potential benefits to participants include improvement or resolution of their pelvic floor pain and pelvic floor disorder symptoms. If found to improve symptoms, cryotherapy can be easily incorporated into the treatment algorithm and started while patients are waiting to begin pelvic floor PT or added to an existing pelvic floor PT regimen. This inexpensive intervention may be especially valuable for patients in resource-poor settings without access to a pelvic floor PT provider. Given rising healthcare costs and limited access to resources like pelvic floor PT for many patients, the addition of vaginal cryotherapy – a simple and inexpensive intervention – holds the promise to transform the treatment algorithm for this common condition and help relieve symptoms for thousands of women.

E Study Design

E1 Overview or Design Summary

This is a placebo-controlled, randomized controlled trial to investigate the role of vaginal cryotherapy on pelvic floor myofascial pain in women. This study involves randomizing patients who are found to have pelvic floor myofascial pain on examination into one of two treatment groups: transvaginal cryotherapy or transvaginal application of a room-temperature tube. Patients will be followed up at two different time points in order to assess response to treatment. Follow-up times include immediately after application (Specific Aim #1) and two weeks following use of the intervention alone (Specific Aim #2). Patients will be referred to pelvic floor PT, which is considered the standard of care for treatment of pelvic floor myofascial pain at this time. As it typically takes 2-3 weeks to get in to see one of the pelvic floor PT providers at Wash U, follow up for this study will be completed prior to their attendance at pelvic floor PT.

E2 Subject Selection and Withdrawal

2.a Inclusion Criteria

Study population and eligibility: All new patients presenting to our facility undergo our standardized pelvic floor myofascial examination and are asked to rate their pain on palpation of the bilateral OI and LA muscles on a 0-10 verbal pain rating scale (0=none 1-3=mild, 4-6=moderate, and 7-10=severe). Patients found to have pelvic floor myofascial pain of at least 4/10 in severity at any of the four sites will be eligible for inclusion. Eligible patients may participate in Specific Aim 1 only or in both Specific Aims 1 and 2.

2.a Exclusion Criteria

Exclusion criteria include age <18, non-English speaking, current diagnosis of dementia, and limited physical mobility that would prevent full participation in pelvic floor PT. Patients will also be excluded if they have performed vaginal cryotherapy in the past or present with a complaint or known history of chronic pelvic pain.

2.b Ethical Considerations

Human Subjects Involvement and Characteristics

We will approach adult women presenting to the FPMRS Clinic at Washington University in St. Louis for inclusion. Eligible women will be ≥18 years old, English speaking, found to have pelvic floor myofascial pain on examination, and willing to participate.

Inclusion of Women, Minorities, and Children

Our patient sample is limited to women. St. Louis City is approximately 50% Black or African American, but our surrounding suburbs and rural areas have a much lower proportion of residents who are African American. We will strive for at least 25% racial/ethnic minority representation in our study (25% African Americans, 1% Asian American, 1% American Indian/Alaska Native). There are no exclusion criteria in this application related to race/ethnicity, however, we will exclude non-English speaking individuals. We do not anticipate this negatively affecting the racial/ethnic minority representation in our study as the proportion of individuals who do not speak English in the St. Louis region is low. We will not include children <18 in our study.

2.c Subject Recruitment Plans and Consent Process

A member of the research team will approach eligible patients and further describe the study. Confidential and informed consent will occur in a private room. Patients will receive verbal and written instructions on using the intravaginal tubes by the research assistant who will not be blinded to treatment allocation. Providers performing the baseline and follow-up pelvic floor myofascial examination and interpreting the data will be blinded to treatment allocation.

2.d Randomization Method and Blinding

Randomization will be in 1:1 allocation to either vaginal cryotherapy or control. The examining physician and study PI will be blinded to treatment allocation. The research assistant will be aware of study allocation in order to provide instruction and answer questions but will not be involved in data collection or analysis.

2.e Risks and Benefits

The risks of the proposed study primarily include discomfort and embarrassment with the pelvic examination. This risk is not unique to study participants as all new patients undergo a comprehensive pelvic floor myofascial examination. Participants may also experience discomfort or embarrassment with intravaginal tube placement. Finally, breach of confidentiality is another risk. Every precaution will be taken to ensure data are kept strictly confidential. Only the research team will have access to paper data, which will be stored in a locked cabinet in the FPMRS offices. Enrolled patients will be assigned unique study identification numbers. A password-protected electronic database will be established using REDCap, and only the research team will have access. No results will be presented in a personally identifiable manner.

2.f Early Withdrawal of Subjects

i When and How to Withdraw Subjects

Patients may request withdrawal from the study at any point. Patients who desire to withdraw from the study will need to inform the research assistant or PI via telephone or

in writing using the contact information in the consent document. Patients who elect to withdraw from the study will not be contacted about future study-related tasks.

ii Data Collection and Follow-up for Withdrawn Subjects

Data collection will stop when the patient requests withdrawal from the study. It is possible, depending on the timing of study withdrawal, that some data collection will have already occurred. This data will be used according to the protocol for data use in the study, however, no further data collection will occur. In the event that a patient withdraws and requests that her previously-collected data be destroyed and not included in the study outcomes, that will be done according to her wish.

E3 Study Intervention

3.a Description

The intervention group will be provided with one vaginal cryotherapy tube, filled with a mixture of isopropyl alcohol (2ml) and water (8ml) that has been kept in the freezer. This mixture results in a "slushy" consistency and prevents the solution from freezing solid thus decreases the risk of discomfort or injury due to the temperature of the tube. They will be instructed to store these tubes in their home freezer.

The control group will be provided with an identical tube that is empty. An empty tube was chosen as the control because a tube with room-temperature liquid may still be perceived as cold.

Patients participating in Specific Aim #1 will insert this tube into the vagina to a comfortable depth. A lubricant will be provided for comfort with tube insertion, if necessary. At the conclusion of the treatment, this tube will be washed thoroughly and given to the patient in a clean plastic baggie for use at home.

Patients in Specific Aim #2 will also be given two tubes according to the group to which they were randomized for use at home.

3.b Treatment Regimen

Both groups will be given the same instructions for use, which will include intravaginal placement of one tube for 10 minutes while resting in a supine position. A lubricant may be used for comfort with insertion.

Patients participating in Specific Aim #1 will perform their first intervention in the office with a repeat examination within 10 minutes of completing therapy. Patients participating in Specific Aims #2 will perform the intervention once daily at home. Patients will be asked to complete a short diary for each session, which will include the time of day, duration of application, pain score prior to and after application, and presence of any pelvic floor disorder symptoms prior to and after application.

3.c Method for Assigning Subjects to Treatment Groups

Randomization will be in 1:1 allocation to either vaginal cryotherapy or control. The examining physician and study PI will be blinded to treatment allocation. The research assistant will be aware of study allocation in order to provide instruction and answer questions but will not be involved in data collection or analysis.

3.d Preparation and Administration of Study Intervention

Cryotherapy and control tubes will be prepared by the investigators and stored on-site until randomization and treatment allocation. The tubes used for the cryotherapy and control interventions are identical, 10 ml conical tubes. Cryotherapy tubes (intervention arm) will be prepared using a mixture of isopropyl alcohol (2ml) and water (8ml) and stored in the freezer. Using this mixture results in a “slushy” consistency and prevents the contents of the tube from freezing solid, thus decreasing the risk of tissue injury. Control tubes will be empty and stored at room temperature.

The appropriate tubes will be distributed by the research assistant with instructions provided for their appropriate use. Patients participating in Specific Aim #2 will be given tubes to take home with instructions to keep the tubes in the freezer or at room temperature according to their treatment assignment. The research assistant will not be blinded to the treatment allocation in order that she may answer any questions related to the intervention.

Patients will self-administer the intervention in the office (Specific Aim #1) or at home (Specific Aim #2) while resting in a supine position for 10 minutes. A lubricant may be used for comfort with tube insertion.

3.e Subject Compliance Monitoring

Patients will be asked to complete a short diary for each session, which will include the time of day, duration of application, pain score prior to and after application, and presence of any pelvic floor symptoms prior to and after application. This survey will be completed electronically via REDCap. The link will be sent via a secure email to the patient at the email addressed provided at the time of enrollment.

3.f Prior and Concomitant Therapy

There will be no requirement for prior therapy in order to participate in the study. Patients will be excluded from participation if they have previously used vaginal cryotherapy. All participating patients will be referred to pelvic floor physical therapy. There is frequently a delay in scheduling pelvic floor physical therapy of up to 2-3 weeks after initial referral thus this time was built into the study procedures in order to assess for the effect of cryotherapy independent of physical therapy. The 2 week follow up visit will occur concurrently or just prior to their first pelvic floor physical therapy visit.

3.g Blinding of Study Drug

The tubes are identical in appearance with the exception of the temperature to touch and contents. The tubes will be distributed to the patients by the research assistant, who is not blinded to treatment allocation. The patients will not be blinded to treatment allocation. The providers, who are blinded to treatment allocation, will not have contact with the tubes once distributed to the patient.

F Study Procedures

F1 Screening for Eligibility

All new patients presenting to our facility undergo our standardized pelvic floor myofascial examination and are asked to rate their pain on palpation of the bilateral OI and LA muscles on a 0-10 verbal pain rating scale (0=none 1-3=mild, 4-6=moderate, and 7-10=severe). Patients found to have pelvic floor myofascial pain of at least 4/10 in severity at any of the four sites will be considered eligible and approached for study inclusion. Exclusion criteria include age <18, non-English speaking, current diagnosis of dementia, limited physical mobility that would prevent full participation in pelvic floor PT, complaint or known diagnosis of chronic pelvic pain or prior use of vaginal cryotherapy. We will enroll a total of 66 patients for the trial.

F2 Schedule of Measurements

Data collection will occur at baseline and 2 weeks (**Figure 2**). Patients will complete validated questionnaires including the short forms of the Pelvic Floor Distress Inventory (PFDI-20), Pelvic Floor Impact Questionnaire (PFIQ-7), and Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire IUGA-Revised (PISQ-IR, 24, 25). Questionnaires will be scored according to published protocols (26, 27).
(see attached)

F3 Safety and Adverse Events

The risks of the proposed study primarily include discomfort and embarrassment with the pelvic examination. This risk is not unique to study participants as all new patients undergo a comprehensive pelvic floor myofascial examination. Participants may also experience discomfort or embarrassment with intravaginal tube placement. Finally, breach of confidentiality is another risk. Every precaution will be taken to ensure data are kept strictly confidential. Only the research team will have access to paper data, which will be stored in a locked cabinet in the FPMRS offices. Enrolled patients will be assigned unique study identification numbers. A password-protected electronic database will be established using REDCap, and only the research team will have access. No results will be presented in a personally identifiable manner.

3.a Safety and Compliance Monitoring

Vaginal cryotherapy is recommended routinely by the physicians and physical therapists in our Division and, to date, no adverse events related to the cryotherapy have been reported. Theoretical adverse events that could be related to use of cryotherapy in the vagina include skin irritation or injury from the temperature of the tube or trauma to the vagina related to placement of the tube.

Patients will be provided with contact information for study personnel who can be reached 24/7 to report an adverse event. At the follow up visit at 2 weeks, patients will be asked whether they experienced any adverse events. Follow up questions will be asked, as appropriate, for patients reporting adverse events during the study period. Adverse events will be monitored and recorded in the REDCap database. Adverse event reporting will occur throughout the duration of the study procedure.

Each reported adverse event will be reviewed by the members of the study team and graded according to the Dindo-Clavien classification for adverse events (see table). (32). Although this classification system is designed for surgical interventions, it is the most applicable classification system currently available for the intervention proposed in this

study. Any Class II or higher complications that are related or possibly related to the study intervention will result in a temporary cessation of enrollment and an investigation by the study team. A determination as to whether the study may resume will be made by the consensus of the study team. If more than 10% of enrolled patients report Class I complications that are related or possibly related to the study intervention, a similar process will occur.

TABLE 1. Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications
	Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

F4 Study Outcome Measurements and Ascertainment

The data collected will include demographic characteristics; basic medical and reproductive health histories; pre- and post-treatment myofascial examination scores; PFDI-20, PFIQ-7, and PISQ-IR results at baseline and follow up visits; PGI-I and SAPS scores at study conclusion; PFPT assessments. Demographic data, medical and reproductive health histories, and pre- and post-treamtnet myofascial examination scores will be obtained from the medical record. Baseline questionnaires will be completed by the patient electronically directly in REDCap using a secure, password-protected tablet owned and operated by the research team. Follow up surveys and questionnaires will be administered electronically as secure surveys built in REDCap.

G Statistical Plan

G1 Sample Size Determination and Power

We expect vaginal cryotherapy to result in at least 3-point improvement in myofascial pain scores as reported on a 0-10 verbal pain rating scale. Prior studies investigating clinically significant reductions in pain scores report greater than 2 points on a 0-10 scale or 30% reduction in pain as clinically significant[28]. In order to detect a 3-point difference with 80% power and alpha 0.05, we would need to enroll 30 patients per group. Accounting for a 20% loss-to-follow up rate, we plan to enroll 33 patients per group for a total of 66 patients. Patients may participate in Specific Aim #1 only, in Specific Aim #2 only, or both Specific Aims. If no patients participate in both Specific Aim #1 and Specific Aim #2, then 132 patients will be required overall.

G2 Interim Monitoring and Early Stopping

This study is designed as a pilot study to test the efficacy and feasibility of vaginal cryotherapy for treatment of pelvic floor myofascial pain. As such, we do not have futility criteria for early stopping. We will monitor for adverse events and pause/stop enrollment for this as indicated above.

G3 Analysis Plan

Specific Aim #1: To determine the effect of vaginal cryotherapy as an immediate treatment modality for patients with pelvic floor myofascial pain**.** *Primary outcome* is change in pelvic floor myofascial pain scores at each site (bilateral OI and LA). The statistical significance of this change between arms will be evaluated by a Students t-test or Wilcoxon rank sum test as appropriate. *Secondary outcomes* include change in PFDI-20, PFIQ-7, and PISQ-IR scores.

Specific Aim #2: To determine the effect of vaginal cryotherapy as a neoadjuvant treatment modality for patients with pelvic floor myofascial pain awaiting pelvic floor PT. *Primary outcome* includes change in pelvic floor myofascial pain scores at each site (bilateral OI and LA) from baseline to follow-up (2 weeks). The statistical significance of this change between arms will be evaluated by a Students t-test or Wilcoxon rank sum test as appropriate. *Secondary outcomes* include change in PFDI-20, PFIQ-7, and PISQ-IR scores, and patient satisfaction (PGI-I, SAPS).

G4 Missing Outcome Data

Patients with missing outcome data for the primary outcome will be excluded from analysis. The primary analysis will be by intention-to-treat with a planned secondary analysis per-protocol. Missing outcome data for secondary outcomes of PFDI-20, PFIQ-7, and PISQ-IR scores will be imputed according to published protcols for imputation of missing data within these questionnaires (26, 27).

H Data Handling and Record Keeping

H1 Confidentiality and Security

In order to ensure the confidentiality of study participants, recruitment and consent will occur in a private examination or consult room. Patients will have ample time to ask questions of the study personnel. Patients will be determined to be eligible based on examination findings at the time of their initial evaluation. Medical record review will occur to confirm eligibility. Study-related activities will occur in a private examination room. Only the research team will have access to paper data, which will be stored in a locked cabinet in the FPMRS offices. Enrolled patients will be assigned unique study identification numbers. A password-protected electronic database will be established using REDCap, and only the research team will have access. No results will be presented in a personally identifiable manner

H2 Case Report Forms and Source Documents

All data will be securely stored in REDCap. Consent documents and hard copy documents will be securely stored in a locked cabinet in the FPMRS offices.

H3 Records Retention

Records of participating patients will be maintained throughout the study and data analysis. Records will be securely destroyed at the earliest possible time after completion of the study. Patients requesting withdrawl from the study and requesting any previously-captured results/data also be destroyed will have this information securely destroyed at the time of receipt of the request.

I Study Administration

I1 Organization and Participating Centers

The Female Pelvic Medicine & Reconstructive Surgery Division at Washington University in St. Louis is organizing and conducting this study. There are no other participating centers.

I2 Funding Source and Conflicts of Interest

This study is being funded by the Female Pelvic Medicine & Reconstructive Surgery Division at Washington University in St. Louis. All study personnel are without conflicts of interest.

I3 Subject Stipends or Payments

Study subjects will not be paid for their participation in this study.

I4 Study Timetable

Participation in this still will occur over 2 weeks. On average, we see about 30 new patients per month. Analysis from our cross-sectional data suggests that pelvic floor myofascial pain of at least 4/10 in severity is present in about 57% of new patients, thus we anticipate enrollment to take approximately 4-8 months, depending on the number of patients who choose to participate in both Specific Aims.

J Publication Plan

We plan to submit the findings from this study for publication in a high-impact Ob/Gyn journal.

K Attachments

K1 Tables

Figure 1: Study flow

K2 Informed consent documents

Informed consent.docx

K3 Patient education brochures

Intervention instructions.docx

K4 Questionnaires or surveys

REDCap daily postPT.docx
REDCap daily prePT.docx
In office pre post.docx
PFDI.pdf
PFIQ.pdf
PGI I.docx
PISQ.pdf
SAPS.docx

L References

1. Sexton CC, Coyne KS, Koop ZS, Irwin DE, Milsom I, Aiyer LP, Tubaro A, Chapple CR, Wein AJ; EpiLUTS Team. The overlap of storage, voiding and postmicturition symptoms and implications for treatment seeking in the USA, UK, and Sweden: EpiLUTS. BJU Int. 2009. 103:12-23.
2. Adams K, Gregory WT, Osmundsen B, Clark A. Levator myalgia: why bother? Int Urogynecol J. 2013; 24: 1687-1693
3. Pastore EA, Katzman WB. Recognizing myofascial pelvic pain in the female patient with chronic pelvic pain. J Obstet Gynecol Neonatal Nurs. 2012; 41(5): 680-691
4. Spitznagle TM, Robinson CM. Myofascial pelvic pain. Obstet Gynecol Clin N Am. 2014; 41: 409
5. Borg-Stein J, Iaccarino MA. Myofascial pain syndrome treatments. Physical Medicine and Rehabilitation Clinics of North America. 2014; 25(2): 357-374.
6. Bedaiwy MA, Patterson B, Mahajan S. Prevalence of myofascial chronic pelvic pain and the effectiveness of pelvic floor physical therapy. J Reprod Med. 2013; 58(11-12): 504-10.
7. Nadler SF, Weingand K, Kruse RJ. The physiologic basis and clinical applications of cryotherapy and thermotherapy for the pain practitioner. Pain Physician. 2004; 7:395-399
8. Abrams P, Cardozo L, Fall M, Griffths D, Rosier P, Ulmsten U, Van Kerrebroeck P, Victor A, Wein A; Standardisation Sub-Committee of the International Continence Society. The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Neurourol Urodyn. 2002; 21: 167-178
9. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, Coyne K, Kelleher C, Hampel C, Artibani W, Abrams P. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol. 2006; 50: 1306-1315

10. Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence, and bladder outlet obstruction. BJU Int. 2011; 108: 1132-1138
11. Kalder M, Pantazis K, Dinas K, Albert US, Heilmaier C, Kostev K. Discontinuation of treatment using anticholinergic medications in patients with urinary incontinence. Obstet Gynecol. 2014; 124: 794-800
12. Latthe P, Latthe M, Say L, Gulmezoglu M, Khan KS. WHO systematic review of prevalence of chronic pelvic pain: a neglected reproductive health morbidity. BMC Public Health. 2006; 6: 177
13. Sedighimehr N, Manshadi FD, Shokouhi N, Baghban AA. Pelvic musculoskeletal dysfunctions in women with and without chronic pelvic pain. Journal of Bodywork and Movement Therapies. 2018; 22:92-96
14. Meister M, Sutcliffe S, Badu A, Ghetti C, Lowder JL. Pelvic floor and obturator internus myofascial pain is common in patients with pelvic floor symptoms. Female Pelvic Med Reconstr Surg. 2017; 23(5): S34
15. Meister M, Sutcliffe S, Badu A, Ghetti C, Lowder JL. Pelvic floor and obturator internus myofascial pain is correlated with lower urinary tract symptom severity. Female Pelvic Med Reconstr Surg. 2017; 23(5): S34
16. Moldwin RM, Fariello JY. Myofascial trigger points of the pelvic floor: associations with urological pain syndromes and treatment strategies including injection therapy. Curr Urol Rep. 2013; 14: 409-417
17. Peters KM, Carrico DJ. Frequency, urgency, and pelvic pain: treating the pelvic floor versus the epithelium. Curr Urol Rep. 2006; 7(6): 450-455
18. Biurrun Manresa JA, Neziri AY, Curaltolo M, Arendt-Nielsen L, Andersen OK. Reflex receptive fields are enlarged in patients with musculoskeletal low back and neck pain. Pain. 2013; 154(8): 1318-24.
19. Fitzgerald MP, Kotarinos R. Rehabilitation of the short pelvic floor I: Background and patient evaluation. Int Urogynecol J. 2003;14:261.
20. Wente KR, Spitznagle TM. Movement-related urinary urgency: a theoretical framework and retrospective cross-sectional study. J Womens Health Phys Therap. 2017; 41(2): 83-90
21. White GE, Wells GD. Cold-water immersion and other forms of cryotherapy: physiological changes potentially affecting recovery from high-intensity exercise. Extrem Physiol Med. 2013; 2:26
22. Ferreira-Junior BJ, Boattaro M, Viera A, Siqueira AF, Vieira CA, Durigan JL, Cadore EL, Coelho LG, Simoes HG, Bemben MG. One session of partial-body cryotherapy (-110 ◦C) improves muscle damage recovery. Scand J Med Sci Sports. 2015; 25(5): e524-30
23. Hohenauer E, Taeymans J, Baeyens JP, Clarys P, Clijsen R. The effect of post-exercise cryotherapy on recovery characteristics: a systematic review and meta-analysis. PLoS One. 2015; 10(9):e0139028.
24. Rogers RG, Rockwood TH, Constantine ML, Thakar R, Kammerer-Doak DN, Pauls RN, Parekh M, Ridgeway B, Jha S, Pitkin J, Reid F, Sutherland SE, Lukacz ES, Domoney C, Sand P, Davila GW, Espuna Pons ME. A new measure of sexual function in women with pelvic floor disorders (PFD): the Pelvic Organ Prolapse/Incontinence Sexual Questionnaire, IUGA-Revised (PISQ-IR). Int Urogynecol J. 2013; 24(7): 1091-1103.
25. Barber MD, Walters MD, Bump RC. Short forms of two condition-specific quality of life questionnaires for women with pelvic floor disorders (PFDI-20 and PFIQ-7). Am J Obstet Gynecol. 2005; 193(1): 103-113.
26. Rockwood TH, Constantine ML, Adegoke O, Rogers RG, McDermott E, Davila GW, Domoney C, Jha S, Kammerer-Doak D, Lukacz ES, Parekh M, Pauls R, Pitkin J, Reid F,

Ridgeway B, Thaker R, Sand PK, Sutherland SE, Espuna-Pons M. The PISQ-IR: considerations in scale scoring and development. Int Urogynecol J. 2013; 24(7): 1105-1122.
27. Barber MD, Kuchibhatla MN, Pieper CF, Bump RC. Psychometric evaluation of 2 comprehensive condition-specific quality of life instruments for women with pelvic floor disorders. Am J Obstet Gynecol. 2001; 185(6): 1388-1395
28. Rowbotham MC. What is 'clinically meaningful' reduction in pain? Pain. 2001; 94: 131-132.
29. Meister MR, Sutcliffe S, Ghetti C, Chu CM, Spitnagle T, Warren DK, Lowder JL. Development of a standardized, reproducible screening examination for assessment of pelvic floor myofascial pain. Am J Obstet Gynecol. 2018. PMID 30527941
30. Meister MR, Shivakumar N, Sutcliffe S, Spitznagle T, Lowder JL. Physical examination techniques for the assessment of pelvic floor myofascial pain: a systematic review. Am J Obstet Gynecol. 2018. PMID 29959930
31. Sutcliffe S, Bradley CS, Clemens JQ, James AS, Konkle KS, Kreder KJ, Lai HH, Mackey SC, Ashe-McNalley CP, Rodriguez LV, Barrell E, Hou X, Robinson NA, Mullins C, Berry SH. Urological chronic pelvic pain syndrome flares and their impact: qualitative analysis in the MAPP network. Int Urogynecol J. 2015; 26(7): 1047-60
32. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004; 240(2): 205-213.