A DOUBLE-BLIND, RANDOMIZED STUDY TO COMPARE ONOBOTULIUMTOXIN A VERSUS KENALOG FOR INTRAVAGINAL TRIGGER POINT INJECTIONS IN THE TREATMENT OF CHRONIC PELVIC PAIN

Principal Investigator: Jamie Bartley, DO

Version Date: August 23, 2017

Study Overview

Background

Chronic pelvic pain (CPP) is a common and often debilitating problem among women. A practical clinical definition of CPP is non-cyclical pelvic pain that is of at least 6 months duration[1]. CPP occurs below the umbilicus and is severe enough to cause functional impairment or require treatment. CPP affects approximately 15% of women and the health care burden is substantial. The direct cost of physician/clinician visits is estimated to be over $880 million and the indirect costs due to lost work is estimated at $555 million[2].

Patients with CPP often go undiagnosed for years and see many different healthcare providers before getting the correct diagnosis and subsequent improvement in their symptoms[3, 4]. Depending on the treating specialists, patients may be diagnosed with bladder pain syndrome/interstitial cystitis (BPS/IC), endometriosis, vulvodynia, or irritable bowel syndrome. A definitive diagnosis may be lacking in up to 60% of patients seeking treatment for CPP[5]. Patients with CPP report that their quality of life is diminished and their relationships with loved ones are often damaged[6, 7]. They may have lost their job as a result of missed work days or inability to function appropriately due to pelvic pain symptoms.

The musculoskeletal system is an important factor in chronic pelvic pain, specifically the persistent and refractory type[8]. Myofascial pain and hypertonic pelvic floor dysfunction are present in as many as 85% of patients with bladder pain syndrome/interstitial cystitis and/or chronic pelvic pain syndromes[9]. The pelvic floor muscles are arranged in deep and superficial layers and act as a sling to support the pelvic organs and the bones and ligaments of the pelvis provide support to the pelvic muscles. The deep levator ani muscles, often referred to as the pelvic diaphragm, are the most important of the pelvic floor muscles and consist of the pubococcygeus, iliococcygeus, and the coccygeus. The main function of the muscles are to control continence and both bowel and urine elimination.

An important concept to understand when treating pelvic pain is that of cross-system interactions. This is a loss of peripheral specificity when a stimulus arrives in the central nervous system making it difficult to sort out the exact source of the stimulus[10]. In the case of pelvic floor dysfunction, the levator muscles may be stretched and irritated but the patient may perceive it as bladder pain or vaginal pain. Studies have

IRB NUMBER: 2015-008
IRB APPROVAL DATE: 09/12/2017

demonstrated that women with CPP had more frequent musculoskeletal findings and had less control over their pelvic floor compared to control subjects[11]. On physical examination, myofascial trigger points have been described. These hyperirritable bands of muscle can be palpated through the vaginal walls. They are often knot- like or taut and are painful on compression, reproducing the patient's pain symptoms[12,13]. Trigger points are thought to be discreet areas of abnormal muscle spasms whereas high-tone pelvic floor muscle dysfunction (HT-PFD) refers to a more global pelvic floor hypertonicity causing diffuse spasm of the levator complex[14]. Both have been implicated in chronic pelvic pain but in our experience, patients with chronic pelvic pain present with more global pelvic floor hypertonia than one area of tenderness as the term trigger point would suggest.

Prior studies of treatments directed towards hypertonic pelvic floor dysfunction in women with CPP have been promising. In a recent NIH-funded multicenter study, investigators found that 59% of patients receiving myofascial physical therapy reported moderate or marked improvement in their symptoms compared to 29% of the control group of patients receiving global therapeutic massage[15]. This and other studies have resulted in pelvic floor physical therapy to be first line treatment of women with chronic pelvic pain and hypertonic pelvic floor dysfunction[16].

In patients that fail non-invasive techniques, intralevator trigger point injections (TPIs) are often the next step. This is often combined with physical therapy and typically requires 3-5 injections to help the muscle relax and return to normal function. Langford and coworkers injected palpable vaginal trigger points with 5cc of a mixture of 10 cc of 0.25% bupivacaine, 10 cc of 2% lidocaine and 1cc of 40 mg triamcinolone[17]. Success, defined as a decrease in pain of 50% or more, occurred in 73% (13/18) with 33% (6/18) being completely pain free.

Intralevator trigger point injections with onabotulinumtoxinA has also been shown to improve pain in patients with chronic pelvic pain and is often the next step following steroid trigger point injections. Typically we use this for patients that respond to steroid TPIs but the effects are not long lasting. OnabotulinumtoxinA has been shown to provide relief for 6-9 months with minimal side effects including, infection, hematoma, and pain all of which are similar to traditional TPI[16].

In a study of 30 patients that received 80 units of onabotulinumtoxinA and 30 patients that received placebo (saline) injection into the pelvic floor muscles for dysmenorrhea, dyspareunia, dyschezia, and nonmenstrual pelvic, there was a significant change in baseline in the onabotulinumtoxinA group in nonmenstrual pelvic pain[18]. Both groups had changes in dyspareunia and pelvic floor pressures (cm H20) but these patients were also allowed to undergo pelvic floor physical therapy during the course of treatment, which may have affected the results in both groups. OnabotulinumtoxinA 150U-400U has also been shown to be very effective in treatment of women with refractory vaginismus[19].

IRB NUMBER: 2015-008
IRB APPROVAL DATE: 09/12/2017

OnabotulinumtoxinA injection has been compared to 80 mg methylprednisone injection in patients with chronic myofascial pain in the piriformis (100u), iliopsoas (150u) or scalenus anterior (80u) muscles and was found to have similar results at 30 days but at 60 days the onabotulinumtoxinA group had statistically significant improvements in their pain scores, compared to the methylprednisone group and also compared to their scores at 30 days[20].

As discussed above, onabotulinumtoxinA is often used for patients that have failed conservative therapy with medications, pelvic floor physical therapy and/or steroid trigger point injections. However, the optimal dosing and frequency of use has not been determined and needs further study. In addition, the effect of onabotulinumtoxinA injections on the need for additional therapy is unclear but may be beneficial for several reasons. First, if relief is able to be maintained over a longer time period initially, patients may be able to avoid having to undergo repeated TPI over 3 to 5 sessions which can be painful, costly, and time consuming and they may progress to needing onabotulinumtoxinA anyway. Second, by providing more immediate and prolonged relief, requirements for other therapies such as pelvic floor physical therapy and narcotic pain medications may be reduced. Third, because many of our patients with pelvic pain present with high tone pelvic floor dysfunction, we expect global intralevator trigger point injections to be more effective than single site injections. Lastly, we know that chronic pelvic pain is associated with anxiety and depression and we hope that the more immediate and prolonged result of onabotulinumtoxinA will provide patients with improved mental health scores.

Objectives and/or Endpoints

The primary objective of this study is **to assess changes in overall pain score using the visual analog scale (VAS) (Appendix 1), the Brief Pain Inventory (BPI) (Appendix 2) and Global Response Assessment (GRA)(Appendix 3) questionnaire at one month** following transvaginal trigger point injections with a steroid (triamcinolone) and a local anesthetic (ropivacaine) vs. onabotulinumtoxinA and a local anesthetic (ropivacaine) in patients with CPP and high-tone pelvic floor dysfunction. We hypothesize that patients in the Botox group will have lower pain scores following treatment and that the treatment will have a longer effect compared to patients in the Kenalog group.

The secondary objective is to determine if there are persistent changes in pain scores using the VAS, BPI, and GRA at 3 and 6 month follow up. Lastly, patients will be asked to complete a questionnaire to determine what other treatments have been needed since the original TPI (Appendix 4).

IRB NUMBER: 2015-008
IRB APPROVAL DATE: 09/12/2017

Patients will be asked to refrain from any additional treatments including pelvic floor physical therapy, or new prescriptions for intravaginal muscle relaxants or narcotic medications during the first month following the initial TPI. If patients are already taking muscle relaxants or narcotics, they will need to either remain stable or decrease the dosage and frequency of the medication. If patients are already receiving pelvic floor physical therapy, they may continue treatment. If patients require increased use of these medications or additional therapies due to worsening or uncontrolled symptoms, these treatments will be provided at the discretion of the treating clinician. These patients will then be evaluated as an intention to treat cohort. In addition, at the one month follow-up visit with the clinician, further treatments will be offered based on the patient's need for further symptom control.

We hope that the information obtained by this study will help guide clinicians to make an evidenced based decision on the clinical efficacy as well as cost effectiveness of two transvaginal trigger point injection protocols for patients with high-tone pelvic floor dysfunction.

Methodology

A randomized, double blind two arm study. Up to 40 women will be included to complete this study. We may enroll up to 60 patients to account for possible dropouts, with each arm having up to 20 subjects. This is a pilot trial and a formal sample size has not been completed. Subjects will be recruited by physician referral or word of mouth. Study activities will take place at the Women's Urology Center in the south tower of Beaumont Hospital, Royal Oak.

Screening

Subjects are eligible to participate in this study if they are a woman greater than 18 years old and have pain localized to the pelvis for greater than 3 months. Overall pelvic pain score must be greater than 4 on the VAS. They will be screened with assessment of last menstrual period (LMP) and a urine pregnancy test. If the woman has had a tubal ligation or a hysterectomy, the pregnancy test will be waived.

A vaginal exam will be performed obtaining a pH and wet mount. If the woman has vaginitis on her wet mount at screening, she may be given a prescription for the appropriate medication per standard of care and be re-screened. She must wait at least 3 days after treatment and may be re-screened once. The vaginal exam will also include a levator exam and the patient must have the finding of high tone pelvic floor dysfunction. This will be determined by the clinician and is defined as diffuse spasms and pain with palpation of the levator complex. Pain scores from 0-10 on the VAS will be recorded according to positions on a clock as rated by the patient (Figure 1).

IRB NUMBER: 2015-008
IRB APPROVAL DATE: 09/12/2017

Informed consent will be obtained from women meeting the screening and inclusion criteria (see below).

Following screening, consent and enrollment, a complete medical history will be obtained and/or confirmed from a prior visit. The intake form will be the same history form that all patient's presenting to the Women's Urology Center are asked to fill out. Information obtained includes demographics, current and past medical conditions, surgical history, social history (smoking, drugs, education, caffeine use, and employment), current medications, and allergies. Past treatment history for pelvic pain including physical therapy, trigger point injections, hydrodistension, cystoscopy, and surgery will be recorded. Subjects in both groups will then be asked to fill out baseline questionnaires including pain score on the VAS and the BPI.

The woman will then be randomized to one of 2 treatment arms in a 1:1 pattern.

Proposed intervention, if applicable (e.g., study visits, surgical procedure, administration of drugs, etc.) or collection of data (e.g., survey, questionnaire, etc.).

Subject enrollment and treatment may both occur at the initial visit. If desired, these visits may also be scheduled as separate visits within a 7-14 day period of time.

The first arm (Group 1) will receive TPI with a steroid and a local anesthetic followed by saline and the second arm (Group 2) will receive a local anesthetic followed by a mixture of 200u of Onabotulinumtoxin A and saline. Each group will receive injections globally throughout the pelvic floor at 1, 3, 5, 7, 9, 11 o'clock (Figure 1). See below.

Intralevator trigger point injections will then be performed as follows: With the subject in lithotomy position and blinded by a drape, the clinician will perform a pelvic exam to palpate the muscles of the levator complex. Pain scores from 0-10 on the VAS will be recorded according to positions on a clock as rated by the patient. The pharmacy will provide the injection medications in dark syringes in the following solutions: For patients randomized to group 1, a mixture of 40mg/1 ml of triamcinolone (40 mg) and 29cc of ropivicaine 0.5% (5cc/6 sites) will be used first followed by 6 cc of saline (1cc/injection site). In Group 2, patients will receive an injection of 30 cc of ropivicaine (5cc/6 sites) followed by a mixture of 200 u of onabotulinumtoxinA and 6cc of saline. In patients weighing less than 58kg, the ropivicaine dose will be adjusted to a maximum of 2.5mg/kg/dose. A 7 inch 22 gauge spinal needle and a needle guide will be used to administer the injections. A tampon will be inserted following the injection for approximately 5 minutes and then removed.

Subjects will be monitored for at least 30 minutes following TPI. An ice pack to the vulva, warm blanket and water or juice will be provided as needed for patient comfort. Side effects will be monitored by assessing vital signs (Blood pressure, pulse, respirations) within 10 minutes of the injection by the clinical staff (medical assistants) and monitoring subject-reported symptoms such as those most commonly noted with trigger point injection such as pain, hematoma, light-headedness, and hypertension (all <1 %). Vital signs and any adverse effects will be reported to the study physician performing the injections. An overall pelvic pain score (0-10) prior to departure will be obtained

For in office follow up visits the following will take place:

30 days (+/- 7 days) following the first TPI, the subjects will return to the WUC for a follow up visit. Follow up questionnaires will be given (VAS, BPI, GRA) and subjects will have an office visit with one of the study clinicians. A pelvic exam will be performed and levator pain scores from 0-10 on the VAS will be recorded according to positions on a clock as rated by the patient. The subject's symptoms will be assessed and other treatments will be initiated as needed.

90 days (+/- 30 days) following the initial TPI, patients will return to the WUC for a follow up visit. Pelvic pain scores will be assessed using the VAS and BPI. GRA will also be determined. Patients will be asked to fill out a questionnaire regarding other treatments they have had since the initial TPI (Appendix 4). A pelvic exam will be performed by the study clinician and levator pain scores from 0-10 on the VAS will be recorded according to positions on a clock as rated by the patient.

At 180 days (+/- 30 days) following the initial TPI, patients will return to the WUC for a follow up visit and a study exit interview. The VAS, BPI, GRA and additional treatments questionnaires will be obtained. A pelvic exam will again be performed by the study clinician and pain scores from 0-10 on the VAS will be recorded according to positions on a clock as rated by the patient.

** While in-person study visits are preferable, the follow up visits may be completed as a phone call visit, if the participant is otherwise unable or unavailable. The questionnaires will be collected via mail.*

<u>In the event the follow up study visit is not conducted in-person, the visit may be conducted by phone and/or mail and Research Staff will:</u>

- Send the follow up questionnaires to the participant for completion with a self-addressed Stamped envelope for questionnaire return
- Review the questionnaires and completion dates with the participant

IRB NUMBER: 2015-008
IRB APPROVAL DATE: 09/12/2017

- Request and verify the completed questionnaires have been returned to the research office
- Contact the participant for clarification and/or to address questions regarding the completed questionnaires, if needed
- Assess concomitant medication changes
- Assess for adverse events

Subjects may be permitted to withdraw from the study if they have poor resolution of their pain or worsening of their symptoms. If they feel that they need other therapy during the first 30 days that is not permitted by the study (additional physical therapy, higher or more frequent doses of vaginal valium or pain medications, repeat TPI, etc.) they may be withdrawn and will be evaluated by the clinician for other treatment options. Patients who withdraw from the study will be asked if they are willing to fill out post questionnaires. Either group can get additional therapy following the first 30 days following the TPI. Furthermore, either group may have repeat TPI with kenalog one month following the original injection but patients may not undergo TPI with onabotulinumtoxinA following the original injection unless they withdraw from the study and are unblinded to prevent overdose of onabotulinumtoxinA. If additional TPIs with kenalog and ropivicaine are indicated at any of the follow up visits, the injections will be prepared and administered in the Woman's Urology Center, per routine standard of care. In no way will their withdrawal from the study impact what treatments will be offered to them. Subjects may also withdraw from the study without any reason given. If they do not feel comfortable continuing treatment by the study clinicians or at the WUC, they will be referred to another provider/site not involved in the study.

IRB NUMBER: 2015-008
IRB APPROVAL DATE: 09/12/2017

Schedule of Activities

	Initial Visit Screening Consent	Treatment Visit Baseline Questionnaires and physical exam (May be done at initial visit)	30 days	90 days	180 days
Screening	X				
Consent	X				
Intake medical history form	X	X (If not done at initial visit)			
Urine pregnancy test[a]	X				
Q tip test	X	X	X[b]	X[b]	X[b]
Vaginal pH and wet mount	X	X (As needed)	X[b] (As needed)	X[b] (As needed)	X[b] (As needed)
Assess concomitant meds	X	X	X	X	X
Vaginal exam assessment for high tone pelvic floor dysfunction with record of patient reported levator pain scores	X	X	X[b]	X[b]	X[b]
Vital signs	X	X	X[b]	X[b]	X[b]
Total overall pelvic pain score on VAS	X	X (done pre and post TPI)	X	X	X
BPI		X	X	X	X
Trigger point injection		X	As needed	As needed	As needed
Assess side effects		X	X	X	X
GRA			X	X	X
Assess concomitant treatments		X	X	X	X

[a]Premenopausal women that have not had a tubal ligation or hysterectomy

[b]Only applies to follow up visits completed in office

Risks and Benefits
The benefit of this study is that it will guide clinicians to make an evidenced based decision on the clinical efficacy as well as cost effectiveness of two different means of intravaginal trigger point injections for patients with PFD. We hope that identification of successful therapies will improve patient's quality of life, decrease the requirement for narcotic pain medications and decrease medical costs to the patient.

In this patient population, pain during the exam and trigger point is common and expected. However, the goal of this treatment is to decrease the pain long term. Anecdotally, patients are able to put up with temporary pain during the treatment to gain the benefit of prolonged relief that comes with injections.

Potential risks to the subject include:

Risks of Trigger Point Injections:
Most Frequent (occurring more than 10% of the time):
- Slight discomfort during the vaginal exam
- Light bleeding at the trigger point injection site
- Pain during the trigger point injection

Rare (occurring less than 1% of the time):
- Vaginal hematoma (collection of blood in the tissue)
- Infection

Risks of OnabotulinumtoxinA:
Less Frequent (occurring from 1% to 10% of the time):
- Transient urinary retention (temporary inability to urinate)
- Transient flatal incontinence (temporary accidental passing of gas)
- Transient fecal incontinence (temporary accidental loss of stool)
- Slight temporary fatigue

Rare (occurring less than 1% of the time):
- Botox toxicity/intolerance
- Lower extremity weakness
- Lower extremity numbness

Risks of Kenalog:
Rare (occurring less than 1% of the time):
- Headache
- Dizziness
- Weight gain
- Hyperglycemia (high blood sugar)
- Trouble Sleeping

IRB NUMBER: 2015-008
IRB APPROVAL DATE: 09/12/2017

Risks of Ropivacaine:
Rare (occurring less than 1% of the time):

- Hypertension (high blood pressure)
- Hypotension (low blood pressure)
- Arrhythmia (abnormal heart rate)
- Tachycardia (rapid heart rate)
- Headache
- Rash
- Lower extremity weakness
- Urinary retention (inability to urinate)
- Urinary incontinence (accidental loss of urine)
- Local anesthetic toxicity (numbing medication could be absorbed through the bloodstream into the rest of the body affecting your breathing, heartbeat, blood pressure)

There is a risk of an allergic reaction from any medication. Symptoms may include swelling, skin rash and/or headache, difficulty swallowing or talking, trouble breathing, muscle weakness. Symptoms can occur days to weeks after injection. There may be unknown side effects or problems that could result in serious illness or even death.

Inclusion Criteria

- Provide informed consent
- Healthy women ≥ age 18 regardless of menopausal status
- Willing and able to fill out study questionnaires. In patients that are unable to read, the research nurse will be available to assist.
- High-tone pelvic floor dysfunction on vaginal exam
- A pelvic pain score of ≥ 4 on screening VAS
- Pain perceived to be in the pelvis that has been present for at least 3 months.

Exclusion Criteria

- Patients that have had Botox to the bladder within the last 8 months
- Patients that have had Botox outside the bladder of ≥ 160 u within the last 12 weeks.
- Patients that have had transvaginal trigger point injections of any form (Botox or steroid) in the last 3 months
- Pregnancy
- Concomitant use of any narcotic drug, alcohol, or any illicit drug use during the study period that could be deemed unsafe in combination with study medication as judged by the investigators.
- Any evidence of vaginitis on wet mount slide at initial visit that is untreated.
- Subject with any other vaginal epithelial disorder that could affect absorption of medication as deemed by the investigators.

IRB NUMBER: 2015-008
IRB APPROVAL DATE: 09/12/2017

- Any indication/condition/medication that the investigators identify as contraindicated in conjunction with study medication.
- Systolic blood pressure > 160 mm Hg on screening blood pressure
- Heart rate > 110 beats/minute on screening heart rate

Randomization

Subjects will be randomized to one of the two trigger point injection types by a sealed randomization envelopes (or similar randomization) created by our biostatistician. Patients will be randomized in a 1:1 pattern in varied randomized block design.

Recruitment

We anticipate recruitment will come from volunteers with pelvic pain both within and outside the Beaumont health care system urology and gynecology practices by physician referral and word of mouth.

Data Analysis

This study is an exploratory pilot study. Descriptive statistics, which will be provided for all variables, will be the main focus of the analysis because of the small sample size. Descriptive statistics will consist of frequency tables and bar charts for categorical variables, as well as summary statistics tables and boxplots for continuous variables.

Exploratory data analysis will be conducted on the data, particularly focusing on comparisons between the two treatment groups. Formal significance testing will be done to analyze group differences in terms of the baseline variables and clinical characteristics at time of treatment.

Since both the VAS and the BPI scores are given on ordinal scales, the marginal distributions of each of these scores will be provided for both time of treatment and 30 days after. For each subject, the difference in their score from pre to post will be calculated. Frequencies will be tabulated for the number of subjects whose pain score improved the number whose pain score stayed the same, and the number whose pain score worsened. The proportion of subjects in these categories will be compared between groups. Bar graphs will be created to illustrate the distribution of this variable. Nonparametric tests may be used to compare groups based on the distribution of the outcome variables.

Data Safety Monitoring Plan

IRB NUMBER: 2015-008
IRB APPROVAL DATE: 09/12/2017

An independent physician (not connected with the study, but familiar with the use of trigger point injections) will review study records at the half-way point of enrollment for each arm of the study to ensure the safety of subjects and lack of significant adverse effects. As an on-going plan, any adverse effects (prolonged bleeding, hemodynamic changes, significant patient pain, or other deemed significant by clinicians) will be reported to the research nurse and then to the PI at the time of the event. Adverse events, serious adverse events, and unanticipated problems not listed in the risks section of this protocol will be reported per federal regulations and IRB guidelines.

Stipend

Participants will receive a check for $15 from William Beaumont Hospital following each of the five study visits. A total stipend of $75 will be paid to those who complete all study visits.

References:

1. Ortiz DD: Chronic pelvic pain in women. *American family physician* 77(11), 1535-1542 (2008).

2. Mathias SD, Kuppermann M, Liberman RF, Lipschutz RC, Steege JF: Chronic pelvic pain: prevalence, health-related quality of life, and economic correlates. *Obstetrics and gynecology* 87(3), 321-327 (1996).

3. Driscoll A, Teichman JM: How do patients with interstitial cystitis present? *The Journal of urology* 166(6), 2118-2120 (2001).

4. Nickel JC, Kaufman DM, Zhang HF, Wan GJ, Sand PK: Time to initiation of pentosan polysulfate sodium treatment after interstitial cystitis diagnosis: effect on symptom improvement. *Urology* 71(1), 57-61 (2008).

5. Zondervan KT, Yudkin PL, Vessey MP, Dawes MG, Barlow DH, Kennedy SH: Patterns of diagnosis and referral in women consulting for chronic pelvic pain in UK primary care. *British journal of obstetrics and gynaecology* 106(11), 1156-1161 (1999).

6. Suskind AM, Berry SH, Suttorp MJ *et al.*: Health-related quality of life in patients with interstitial cystitis/bladder pain syndrome and frequently associated comorbidities. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* (2012).

7. Nickel JC, Tripp DA, Pontari M *et al.*: Psychosocial phenotyping in women with interstitial cystitis/painful bladder syndrome: a case control study. *The Journal of urology* 183(1), 167-172 (2010).

8. Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W: Idiopathic pain disorders--pathways of vulnerability. *Pain* 123(3), 226-230 (2006).

9. Peters KM, Carrico DJ: Frequency, urgency, and pelvic pain: treating the pelvic floor versus the epithelium. *Current urology reports* 7(6), 450-455 (2006).

10. Bielefeldt K, Gebhart GF: Textbook of pain. (5th). Elsevier, 721-736 (2006).

11. Tu FF, Holt J, Gonzales J, Fitzgerald CM: Physical therapy evaluation of patients with chronic pelvic pain: a controlled study. *American journal of obstetrics and gynecology* 198(3), 272 e271-277 (2008).

12. Alvarez DJ, Rockwell PG: Trigger points: diagnosis and management. *American family physician* 65(4), 653-660 (2002).

IRB NUMBER: 2015-008
IRB APPROVAL DATE: 09/12/2017

13. Janicki TI: Chronic pelvic pain as a form of complex regional pain syndrome. *Clinical obstetrics and gynecology* 46(4), 797-803 (2003).

14. Goldstein AT, Burrows LJ, Kellogg-Spadt S: Intralevator injection of botulinum toxin for the treatment of hypertonic pelvic floor muscle dysfunction and vestibulodynia. *J Sex Med* 8 (5): 1287-90 (2011).

15. Fitzgerald MP, Payne CK, Lukacz ES *et al.*: Randomized multicenter clinical trial of myofascial physical therapy in women with interstitial cystitis/painful bladder syndrome and pelvic floor tenderness. *The Journal of urology* 187(6), 2113-2118 (2012).

16. Butrick, CW. Pelvic floor hypertonic disorders: identification and management.*Obstet Gynecol Clin North Am* ;36(3):707-22 (2009).

17. Langford CF, Udvari NS, Ghoniem GM. Levator Ani Trigger Point Injections: An Underutilized Treatment for Chronic Pelvic Pain. Neurourol Urodyn 26(1):59-62 (2007).

18. Abbott JA, Jarvis SK, Lyons SD, Thomson A, Vancaille TG. Botulinum Toxin Type A for Chronic Pain and Pelvic Floor Spasm in Women: a Randomized Controlled Trial. *Obstet Gynecol* 108 (4): 915-23 (2006).

19. Ghazizadeh S, Nikzad M. Botulinum toxin the the treatment of refractory vaginismus. Obstet Gynecol. Nov: 104 (5 Pt 1): 922-5 (2004).

19. Porta M. A comparative trial of botulinum toxin type A and methylprednisolone for the treatment of myofascial pain syndrome and pain from chronic muscle spasm *Pain* 85 (1-2):101-5 (2000).

IRB NUMBER: 2015-008
IRB APPROVAL DATE: 09/12/2017