

2018

Examining the role of comorbid factors in the development of central sensitization with chronic pelvic pain in cases of adolescent endometriosis

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**EXAMINING THE ROLE OF COMORBID FACTORS IN THE DEVELOPMENT
OF CENTRAL SENSITIZATION WITH CHRONIC PELVIC PAIN IN CASES
OF ADOLESCENT ENDOMETRIOSIS**

by

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B.S., American University, 2013

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science

2018

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DEDICATION

I would like to dedicate this work to the young women participating in the Women's Health Study. It is because of your commitment and generosity that this research is possible. Thank you.

ACKNOWLEDGMENTS

To everyone who has supported me through this experience, I extend my wholehearted appreciation and gratitude. Your support allowed me to succeed personally and professionally and for that I thank you.

I would like to thank Dr. Christine Sieberg and the staff of the Biobehavioral Pediatric Pain Lab at Boston Children's Hospital for their continuous support this year. Dr. Sieberg's unwavering confidence in my chosen topic and support of my professional development defined my research experience. I could not have asked for a more supportive group of women to work with – Elena, Hannah and Jacqueline, you have become close friends this year and I look forward to your future successes; and Cindy – thank you for always knowing the solution and being so willing to help.

To my family and friends: thank you for understanding how important these last two years have been for me; for trusting my decisions and constantly supporting me. Especially my mom, who instilled in me the love of medicine, taught me empathy and compassion and has never stopped supporting me – thank you for everything, it has made all the difference.

D.B., B.H., R.H., L.O., A.G., E.G., M.K.,

M.N., L.M., C.D., N.P., G.E., L.D., G.O.

– Thank you.

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ABSTRACT

Objectives: This study aims to better understand the relationship between psychosocial factors and the development of chronic pelvic pain (CPP) in cases of adolescent endometriosis, specifically mood disorders, pain catastrophizing and quality of life, and to detect the development of central sensitization within this population.

Methods: Eligible candidates were patients between 14 and 22 years old with confirmed diagnosis of endometriosis and chronic pelvic pain who were enrolled in the Women's Health Study: From Adolescence to Adulthood through the Boston Center for Endometriosis (BCE) and Boston Children's Hospital. The administration of quantitative sensory testing (QST) to assess mechanical touch perception, pressure pain sensitivity and temporal summation was performed on 48 subjects. Pre-surgical baseline surveys, which included pain catastrophizing and quality of life measures, were obtained from the BCE. Record of diagnosed mood disorder (anxiety/depression) was obtained through medical chart review. Pearson correlations between QST measures, pain catastrophizing, presence of mood disorders or central sensitization and pre-surgical pain scores were conducted. One-way ANOVA calculations, and one sample and paired t-tests were conducted to gain further understanding of these variables as they relate to groups within the cohort.

Results: Regarding QST measures, 23 subjects (47.9%) produced a wind-up phenomenon from temporal summation during QST administration, which serves as a surrogate for the presence of central sensitization (+CS). Pressure sensation and pain scores correlated at all test sites (lower and upper abdomen, as well as finger control site) and wind-up phenomenon correlated in the lower and upper abdomen throughout the cohort. For the presence of mood disorders, anxiety and depression were equally distributed across the +CS and –CS groups. Review of pre-surgical pain scores and pain catastrophizing (PCS) within the cohort had significant correlations between pre-surgical pain and PCS subsets of rumination and magnification. PCS total and subset scores also correlated to +CS. One-way ANOVA calculations showed the cohort as a whole presented with clinically significant helplessness.

Conclusions: Results encourage further investigation of the relationship between endometriosis, comorbid conditions, environmental factors and the development of CPP within the adolescent population. More detailed data regarding mental health and documentation of condition progression, as well as establishment of health control values and sample growth are encouraged for the continued progress of this project.

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LIST OF ABBREVIATIONS

A2A	Women’s Health Study: From Adolescence to Adulthood
ANOVA	One-way Analysis of Variance
ASRM	American Society for Reproductive Medicine
BCE	Boston Center for Endometriosis
BCH	Boston Children’s Hospital
BPPL	Biobehavioral Pediatric Pain Lab
BWH	Brigham and Women’s Hospital
CBT	Cognitive Behavioral Therapy
CPP	Chronic Pelvic Pain
CS	Central Sensitization
DFNS	German Research Network on Neuropathic Pain
DOS	Day of Surgery
GnRH α	Gonadotropin Releasing Hormone Agonist
NSAID	Nonsteroidal Anti-inflammatory Drug
PCS	Pain Catastrophizing Scale
PSQ	Pain Sensitivity Questionnaire
QST	Quantitative Sensory Testing
SF-36	Short Form Health Survey
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor

INTRODUCTION

Endometriosis, defined as the presence of endometrial-type mucosa outside the uterine cavity, is a gynecological disease affecting up to 17% of reproductive-aged women (Stuparich, Donnellan, & Sanfilippo, 2017; Vercellini, Viganò, Somigliana, & Fedele, 2014). The growth of endometrial tissue, which serves as the site of embryonic implantation within the uterine cavity, outside the standard anatomical location, can lead to dysmenorrhea, dyspareunia, chronic pelvic pain and infertility (Vercellini et al., 2014). Although most commonly diagnosed in adult women, endometriosis is also present in postmenarcheal adolescents with similar symptoms including painful or heavy menstruation, and bowel and bladder dysfunction (Young, Fisher, & Kirkman, 2017). Of note, a study by Stuparich et al. noted that two-thirds of surveyed women diagnosed with endometriosis in adulthood presented with symptoms of disease before the age of 20, suggesting earlier diagnosis is possible and beneficial (Stuparich et al., 2017). While adult cases of endometriosis have a typical cyclic pain presentation, one study found only 9.4% of adolescents presented with cyclical pain symptoms when surveyed (Marc R Laufer, Sanfilippo, & Rose, 2003). The acyclic nature of adolescent symptoms is a common cause of delayed diagnosis and can lead to chronic pelvic pain, central sensitization, infertility and further disease progression (DiVasta, Vitonis, Laufer, & Missmer, 2017); elucidating these factors is the aim of the present study.

Endometriosis: Symptoms, Diagnosis and Treatment

The standard approach to confirming a diagnosis of endometriosis is laparoscopic investigation with surgical excision of endometrial lesions. Visualization of ectopic endometrium is not sufficient for diagnosis (Shin & Howard, 2011). Risk factors for disease prior to presentation of dysmenorrhea include family history, early menarche, history of asthma, obstructive Mullerian anomalies, and previous surgical history (Matalliotakis et al., 2017; Stuparich et al., 2017). In a study of 20 adolescents in New Zealand, 30% of participants had confirmed first relatives with an endometriosis diagnosis (Roman et al., 2010). Typical presentation in adolescents is mild, with some studies finding only stage I and II lesions among participants (M. R. Laufer, Goitein, Bush, Cramer, & Emans, 1997). However, a systematic review found that 32% of participants in eight of the 15 included studies had moderate to severe endometriosis (Janssen, Rijkers, Hoppenbrouwers, Meuleman, & D'Hooghe, 2013). It is clear that although symptoms vary, the progression of disease to all stages, including deep endometriosis and ovarian endometriomas, is possible within the adolescent population and further supports the need for early detection of disease (Saridoğan, 2015).

Diagnosis of endometriosis during laparoscopic surgery includes the staging of disease using the American Society for Reproductive Medicine (ASRM) numerical classification system. Using this method, endometriosis can range from stage I (minimal) to stage IV (severe) disease. This assessment includes analysis of both extent and depth of lesions as well as lesion quality (Doyle, Missmer, & Laufer, 2009). A weighted assessment score determines stage of disease, taking into account size (<1cm, 1-3cm,

>3cm), type (superficial/deep, filmy/dense), and color (red [red, red-pink, flame-like, vesicular blobs, clear vesicles], white [white, yellow-brown, peritoneal defects], or black [black and blue lesions]) including percent of each lesion type (American Society for Reproductive Medicine, 1997). Photographs and diagrams are provided by the ASRM to improve staging accuracy.



**AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION OF ENDOMETRIOSIS**

Patient's name _____ Date _____
 Stage I (Minimal) - 1-5 Laparoscopy _____ Laparotomy _____ Photography _____
 Stage II (Mild) - 6-15 Recommended treatment _____
 Stage III (Moderate) - 16-40
 Stage IV (Severe) - >40 Prognosis _____

ENDOMETRIOSIS		<1 cm	1-3 cm	>3 cm
Peritoneum	Superficial	1	2	4
	Deep	2	4	6
Ovary	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
POSTERIOR CULDESAC OBLITERATION			Partial	Complete
			4	40
Ovary	ADHESIONS	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
Tube	R Filmy	1	2	4
	Dense	4*	8*	16
	R Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Figure 1: American Society for Reproductive Medicine Endometriosis Classification Guidelines. Used during laparoscopic procedure to determine stage of endometriosis based on type of excised lesions. Stuparich, M. A., Donnellan, N. M., & Sanfilippo, J. S. (2017). Endometriosis in the Adolescent Patient. *Seminars in Reproductive Medicine*, 35(01), 105.

Low levels of pelvic pain associated with menses are commonly treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Oral contraceptives are alternatives to adverse menstruation symptoms and provide the additional benefit of protection against

unwanted pregnancy. Pain that is resistant to these treatment methods should be considered suspicious and raise concern for possible presence of endometriosis. It is also important to note that even if the standard treatment methods succeed the presence of symptoms associated with endometriosis should not be dismissed as further disease development is still possible (Saridoğan, 2015). Persistent pelvic pain resistant to treatment also supports the need for visual investigation of the abdominal cavity, where a diagnosis of endometriosis can be confirmed.

Although removal of all visualized lesions during the laparoscopic procedure should eliminate the presence of symptoms, including pelvic pain, recurrence of endometrial lesions is possible. Treatment for lesion recurrence is primarily further surgical excision and the adjustment of standard treatment methods (hormonal therapy via oral contraceptive or intrauterine device) to match current symptoms. As endometriosis is an estrogen-driven disease, the use of gonadotropin releasing hormone agonists (GnRHAs), which suppress the production of estrogen, is recommended for recurrent or severe cases of disease with the hope of slowing lesion growth and reducing symptoms. There is concern, however, with the use of GnRHAs by adolescent patients due to the loss of bone density that accompanies reduced estrogen levels (Zito et al., 2014). GnRHAs also have the risk of side effects, including mood swings/depression and substantial weight gain. Similarly, the use of intrauterine devices (IUDs) is not recommended in virginal patients, therefore having limited use within the adolescent population (Saridoğan, 2015; Zito et al., 2014). Ultimately, the inability to successfully

treat pain symptoms related to endometriosis gives concern to the development of comorbid conditions, such as anxiety and depression.

Chronic Pelvic Pain as Related to Endometriosis

The varied presentation of endometriosis-related symptoms in adolescents can lead to delayed diagnosis and development of secondary conditions including chronic pelvic pain (CPP) (DiVasta et al., 2017). Defined as non-malignant pain sensation in structures of the pelvis, CPP must present either continuously or recurrently for longer than six months (Baranowski, 2009; Brawn, Morotti, Zondervan, Becker, & Vincent, 2014). Ahead of pelvic congestion and vulvodynia/vaginitis/vulvar vestibulitis, endometriosis is the leading reproductive tract-related cause of and affects almost 40% of adolescents with CPP (Stein, 2013; Stuparich et al., 2017; van Aken et al., 2017). Typical findings accompanying a diagnosis of CPP include: symptoms present for at least six months, incomplete relief despite treatment, significant decrease in physical functioning, signs of depression (lack of quality sleep, weight loss, loss of appetite), hypersensitive response to nociceptive stimuli and altered family roles (Steege & Siedhoff, 2014). Whereas acute pain resolves with treatment and healing of the stimulated area, chronic pain is not as clearly understood nor does it respond to a standard treatment plan (Stein, 2013). As of 2013, it is estimated that 9 million women in the United States between the ages of 18 and 50, or roughly 15% of the female adult population, have CPP (Stein, 2013).

Pain is a subjective experience, making factors like pain catastrophizing, characterized by magnification, rumination and exaggerated emotions due to anticipated or ongoing pain (Kapoor, Thorn, Bandy, & Clements, 2015; Pielech et al., 2014), and pain anxiety important references for understanding pain perception (van Aken et al., 2017). Driven by Melzack's Neuromatrix Theory which introduced the idea of neuroplasticity, or the concept of experiences shaping the future processing of sensory signaling by the central nervous system (Melzack & Katz, 2012), the explanation for chronic pelvic pain has expanded to include the development of allodynia, or the evolution of pain perception to non-painful stimuli, and the exaggerated reaction to a painful stimuli, known as hyperalgesia (Steege & Siedhoff, 2014). Based on this expansion of understanding, to define the pain experience as a purely physical stimulation is an oversimplification of the pain sensation. Within patients with endometriosis, the laparoscopic findings commonly do not correlate to the severity of pain reported by the patient, providing further evidence that a singularly physical cause of pain is unlikely (Milingos et al., 2006; Steege & Siedhoff, 2014). Another point of interest through laparoscopic intervention is the degree of pain level variation reported by patients with similar pathological findings.

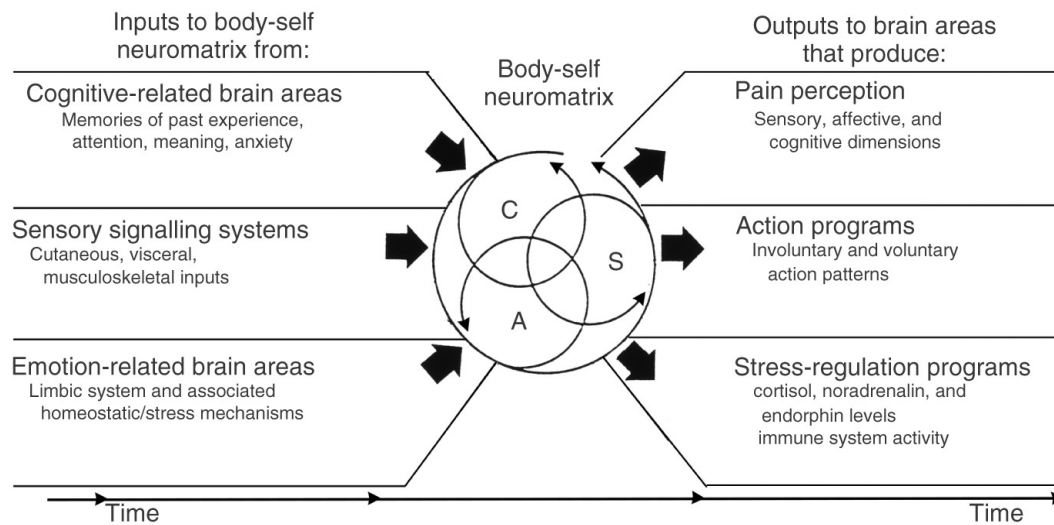


Figure 2: Melzack’s Neuromatrix Theory of chronic pain. A representation of the factors influencing the pain experience and layering of pain signaling within the body Melzack, R., & Katz, J. (2012). Pain. *Wiley Interdisciplinary Reviews: Cognitive Science*, 4(1), 5.

Assessment of Chronic Pain

Understanding the relationship between endometriosis and CPP is necessary to improve the treatment of the affected population; however the subjective nature of the pain sensation and classification of pain symptoms by researchers impose limitations on available testing techniques (Cruz-Almeida & Fillingim, 2014). Based on the current hypothesis of pain syndromes, which proposes that different clinical signs reflect unique pathophysiological origins of pain generation (Rolke et al., 2006), it is believed the work of many pain signals from different symptoms come together to produce the unique pain characteristics of chronic conditions. Animal model data supports this idea through the demonstration of characteristic sensory symptoms produced by multiple mechanical stimuli working in harmony (Rolke et al., 2006; C. J. Woolf & Salter, 2000). To bridge the mechanism-based hypothesis of pain syndromes from animals to human subjects, the

German Research Network on Neuropathic Pain (DFNS) was founded with the goal of building a database of neuropathic pain states categorized by patient phenotype, or observable characteristics. Using a standardized quantitative sensory testing (QST) technique, the DFNS was able to establish baseline parameters for the use of QST on patients with neuropathic pain conditions, including chronic pelvic pain (Rolke et al., 2006).

The QST protocol includes seven tests measuring 13 parameters in response to sensory stimuli in order to characterize somatosensory functioning (Cruz-Almeida & Fillingim, 2014; Rolke et al., 2006). For clinical administration, the tests can be grouped as 1) thermal detection thresholds for the perception of cold, warm and paradoxical heat sensations, 2) thermal pain thresholds for cold and hot stimuli, 3) mechanical detection thresholds for touch and vibration, and 4) mechanical pain sensitivity including thresholds for pinprick and blunt pressure, stimulus/response-functions for pinprick sensitivity and dynamic mechanical allodynia, and pain summation to repetitive pinprick stimuli (wind-up like pain) (Rolke et al., 2006). The QST protocol provides the detection and pain thresholds of the participant, which indicates their sensitivity level. Wind-up like pain represents increased pain perception to repeated stimuli when compared to singular stimuli of the same value in the same location, an indicator of abnormal neurological sensory processing known as central sensitization (Rolke et al., 2006).

Central Sensitization

Central sensitization is the concept that repeated low-level stimuli may result in a stronger central perception of pain over time (Steege & Siedhoff, 2014). Discovered and

defined by Clifford Woolf, M.B., B.Ch., Ph.D., M.R.C.P., central sensitization (CS) develops after peripheral stimulation by noxious stimuli. With time, the spinal cord develops a strong, centralized response to normal input from a general region. The phenomenon is believed to include both an increase in synaptic strength as well as a reduction of inhibitory signaling in the nerves of the spinal cord. In addition to noxious stimulation, CS can develop after peripheral inflammation and injury to the spinal cord or higher brain center (C. J. Woolf & Salter, 2000). It is also understood to be responsible for secondary hyperalgesia, or the spread of increased pain sensitivity to an area beyond that of injury, and allodynia, or heightened pain response to light touch stimulation (Clifford J. Woolf, 2007). The discovery of CS has allowed new pain treatment methods to emerge. Rather than removing the pain stimulus, which proved unsuccessful for cases of CS due to centralized versus peripheral changes, the focus has turned to normalizing the centralized response (Clifford J. Woolf, 2007).

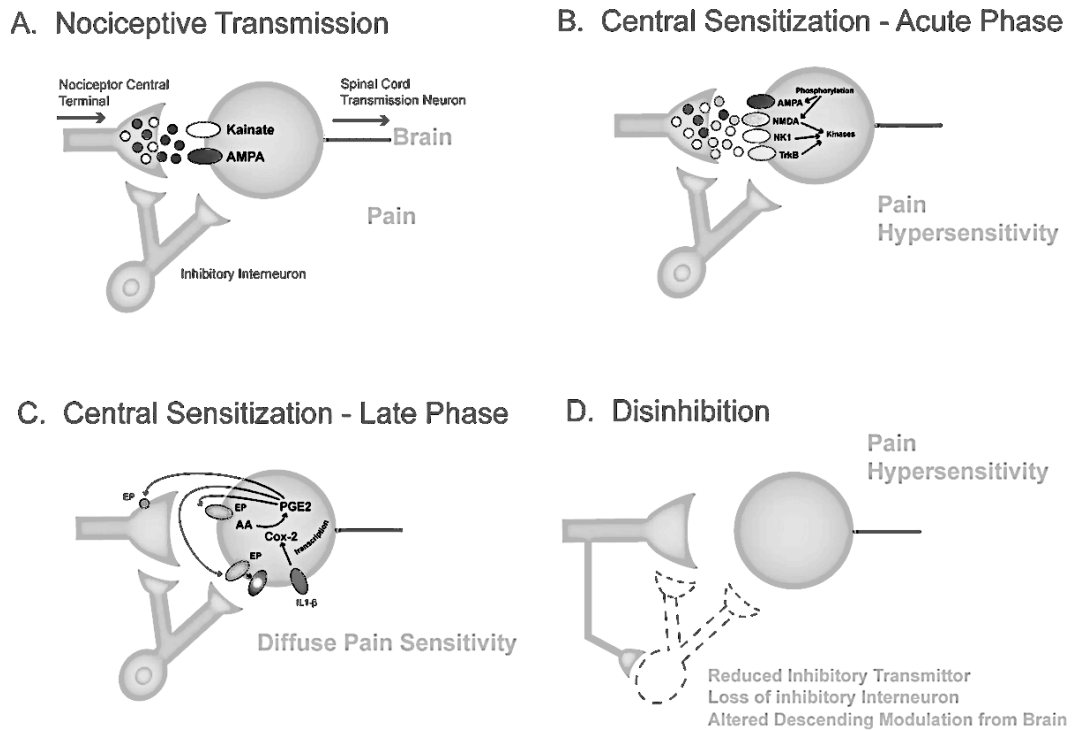


Figure 3: Development of Central Sensitization Phenomenon. Originating from a peripheral stimulus, acute central sensitization includes hypersensitivity at the synapse, followed by diffuse sensitivity during the late phase of development. Full development of central sensitization presents as a loss of sensory inhibition and increased pain perception. Woolf, Clifford J. (2007). Central Sensitization Uncovering the Relation between Pain and Plasticity. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, 106(4), 866.

The idea of a centralized overreaction to painful stimuli helps explain the incorporation of multiple organ systems in the causation of CPP. Peripherally there is no sharing of sensory information, however, with central changes a generalized heightened response develops, which is thought to generate perceived effects across multiple organ systems. Although viewed as a peripheral condition, CPP is clearly associated with changes of the central nervous system when compared to a healthy, pain-free population (Brawn et al., 2014). Understanding how and why central sensitization appears in certain patients and not others is the next step in approaching treatment and prevention strategies

for CPP. Symptoms should be treated regardless to origin, as the ability to reverse central changes is unknown and pain is thought to exacerbate over time (Brawn et al., 2014).

Mood Disorders in Adolescents

A systematic review of 18 studies concerning endometriosis in relation to psychiatric symptoms found the disease associated with some aspect of reduced mental health, quality of life, or type of psychological symptom (Pope, Sharma, Sharma, & Mazmanian, 2015). Of those surveyed, 56.4% (44/78) of women with endometriosis had symptoms which qualified as a mental disorder, compared to 43.6% (48/110) of healthy controls. Based on the findings, it was suggested that women who present with symptoms of endometriosis should be screened for psychological disorders (Pope et al., 2015). Within mental health disorders, anxiety and depression are the most common comorbid diagnoses of endometriosis (Friedl et al., 2015; Laganà et al., 2017; Pope et al., 2015; Vitale, Rosa, Rapisarda, & Laganà, 2017). In a review of comorbidities in patients with endometriosis, 48% of participants (n=138) had depression and/or anxiety and 35% of participants had a mood disorder as well as a comorbid pain condition (Smorgick, Marsh, As-Sanie, Smith, & Quint, 2013). Prevalence of mood disorders was highest when combined with pain disorders, which although did not include CPP, highlights the relationship between mood disorders and chronic pain. The presence of anxiety or depression in adolescents diagnosed with endometriosis can reduce their coping mechanisms and place them at a disadvantage during the development of CPP (Smorgick et al., 2013). Evidence suggests that the presence of mood disorders may increase

perception of pain signaling, which then amplifies the cycle of chronic pain development associated with disease (Cavaggioni et al., 2014; Laganà et al., 2017).

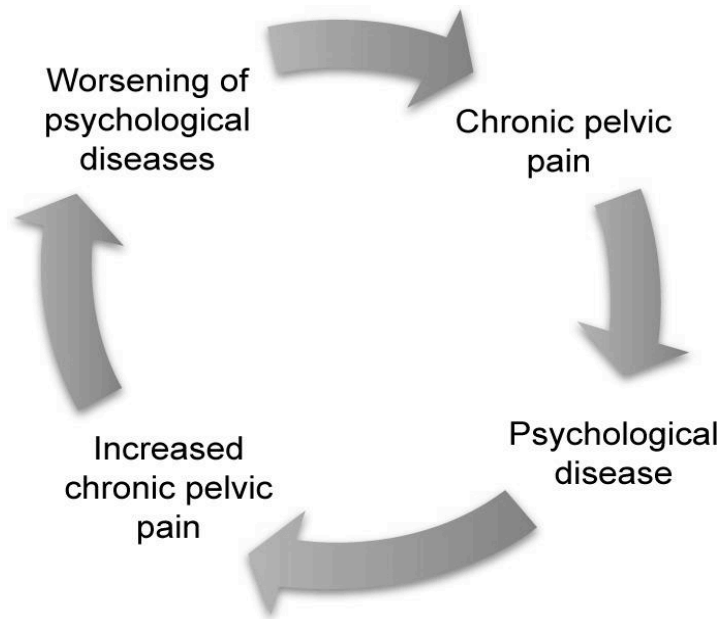


Figure 3: Cyclic relationship between chronic pelvic pain and psychological disease. Laganà, A. S., La Rosa, V. L., Rapisarda, A. M. C., Valenti, G., Sapia, F., Chiofalo, B., ... Vitale, S. G. (2017). Anxiety and depression in patients with endometriosis: impact and management challenges. *International Journal of Women's Health*, 9, 328.

Mood disorders have been frequently detected among the CPP patient population, either as a cause, consequence or simultaneous occurrence (Pereira, França, de Paiva, Andrade, & Viana, 2017). The timing of psychological diagnosis as a comorbidity of chronic pelvic pain has not been clearly tracked and the question of premorbid psychological issues versus those subsequent to chronic pelvic pain still remains (Baranowski, 2009). By itself chronic pelvic pain is difficult to diagnose due to the subjective nature of symptom perception and similarities to other comorbid conditions, especially depression (Pereira et al., 2017). Negative connotation towards mood disorders

or the perception thereof within the adolescent population may also present as a limiting factor in understanding the mood disorder/ CPP relationship. Diagnosis and further understanding of mood disorders in relation to CPP should be approached on an individual level, gaining an understanding of the patient's coping mechanisms, rather than applying standardized protocol to all presenting patients (Steege & Siedhoff, 2014).

Cognitive behavioral therapy (CBT) and pharmacotherapy, specifically selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines, are standard treatment recommendations for adolescents and adults with anxiety and depression. However, pharmacotherapy should be utilized only when necessary. Although the National Institute of Mental Health concluded in 2007 that the drug benefits outweigh the risks (Bridge et al., 2007), SSRIs are known to increase the risk of suicidal thoughts or behavior in adolescents. Physical activity has also been used as a therapeutic measure and has shown positive outcomes when used among adolescent populations, especially within overweight and obese patients (Vancini et al., 2017). Barriers to this treatment option include the inability to engage in exercise due to pain symptoms, which limit its effectiveness within the target population. Within endometriosis, SSRIs have taken on a multifaceted role. As the use of GnRHAs for cases of severe endometriosis becomes more prevalent in adolescent populations, attention has been taken to the unwanted development of anxiety and depression as severe side effects (Warnock, Bundren, & Morris, 1998). A study comparing the efficacy of SSRI therapy in conjunction with the use of GnRHAs showed no improvement in pain scores beyond sole use of GnRHAs, however, it did show a significant improvement in mental health and suggests the use of

SSRIs can help manage side effects of otherwise effective treatment methods (Warnock et al., 1998).

Specific Aims and Objectives

Chronic pelvic pain plays a critical role in the treatment and management of endometriosis, influencing procedure and medication decisions that affect progression of disease and patient wellbeing. The aim of this study is to understand the relationship between psychosocial factors and the development of chronic pelvic pain in cases of adolescent endometriosis. By establishing this relationship, it is then possible to investigate the development of central sensitization within this cohort. As central sensitization implies heightened nervous system response, it is thought that other disorders associated with neurological functioning, including anxiety and depression may influence the development of this condition and other comorbid factors.

- *Aim 1a:* To determine the occurrence of wind-up temporal summation, which is a surrogate for central sensitization, in an adolescent and young adult cohort of patients with surgically confirmed endometriosis.
- *Aim 1b:* To determine if the presence of mood disorders is related to pain sensitivity and if it is greater in patients with central sensitization.
- *Hypothesis #1:* Participants with diagnosed mood disorders will have greater pain sensitivity, lower pain thresholds, and a higher occurrence of central sensitization compared to participants without mood disorders.
- *Aim 2:* To compare quality of life and pre-surgical pain catastrophizing measures in patients with endometriosis to determine whether the presence of central

sensitization and/or mood disorders impacts quality of life and pain catastrophizing.

- *Hypothesis #3*: The presence of anxiety, depression and central sensitization in patients with endometriosis will be higher in those demonstrating pre-surgical pain catastrophizing and will negatively relate to quality of life measures.

METHODS

This study was conducted by the Biobehavioral Pediatric Pain Lab (BPPL) at Boston Children's Hospital (BCH), in conjunction with the Boston Center for Endometriosis (BCE), and looked to identify the presence of central sensitization in adolescent and young women diagnosed with endometriosis. Participants were women enrolled in the Women's Health Study: From Adolescence to Adulthood (A2A), a prospective, longitudinal study through the BCE that conducts deep phenotyping of endometriosis. All patients enrolled in A2A are evaluated by and operated on the BCE, thus the participants in this study received diagnosis confirmation and follow-up treatment of endometriosis by the same physician, director Dr. Marc Laufer.

Recruitment

- Participation in the study is based on multiple factors and recruitment uses IRB-approved techniques to enroll subjects. Eligible women must be enrolled in the BCE's Women's Health Study: from Adolescence to Adulthood program, be between the ages of 14 and 22, and have a diagnosis of endometriosis (confirmed via laparoscopic investigation). Potential participants presented to either the outpatient clinic in the Department of Gynecology and Adolescent Medicine at Boston Children's Hospital in Boston or outpatient offices at Boston Children's at Lexington. Prior to clinic arrival, research assistants at the BCE screened patients enrolled in the A2A program for eligibility in this study. BPPL research interns approached potential participants upon checking into the clinic to obtain initial

consent and assent from interested patients and parents, when applicable. In the case of a schedule conflict with an interested patient, BPPL contact information was given and patients received a follow-up phone call to schedule a time to participate in the study.

Measures

Pre-surgical Baseline Survey

- All participants of the Women's Health Study: A2A are asked to complete a baseline survey provided by the BCE upon enrollment. With the purpose of collecting information to generate symptomatic changes among participants, the baseline survey was completed by 45 of the 46 total participants in the study before undergoing a laparoscopic procedure for confirmation of endometriosis. Participants completed the survey at home or during a visit to BCH or Brigham and Women's Hospital (BWH), and were given the option to use a tablet/computer or to complete via written questionnaire. The baseline survey has been amended multiple times since its creation, due to the longitudinal nature of A2A and desire for questions that provide current information. Several versions of the survey were used by study participants and careful consideration was taken when retrieving responses to specific prompts to ensure accuracy across the cohort. Unfortunately, this variation also led to incomplete data collection. The baseline survey contains a series of questions regarding participant demographics, menstruation and reproductive history, pelvic pain and pain associated with

menstruation, medical and family history, lifestyle choices and sun exposure.

Questions from the 36-Item Short Form Health Survey (SF-36), a questionnaire designed to measure health and wellbeing from the patient's point of view, were also used to gauge participant quality of life.

- Short Form Health Survey (SF-36): Developed by RAND Corporation, the SF-36 is a generic series of questions intended to provide details on one's quality of life as a way to measure patient outcomes and treatment efficacy (J. E. Ware & Sherbourne, 1992). Due to its self-reporting nature, the SF-36 was developed to be a logical series of situations grouped by presenting scenario to be answered using a numerical scale. The eight categories highlighted in the SF-36 include physical abilities (e.g. "How does your physical health limit you from bending, kneeling or stooping?"), limitations due to physical health (e.g. "Were you limited in the kind of work or other activities as a result of your physical health?"), limitations due to emotional health (e.g. "During the past four weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups?"), presence of pain (e.g. "How much physical pain have you had in the past four weeks?"), emotional wellbeing (e.g. "During the past four weeks, have you been a very nervous person?"), social interactions and limitations (e.g. "During the past four weeks, how much of the time has your physical health or emotional problems interfered with your social activities?"), general health comprehension (e.g. "How true or false are the following statements to you: I seem to get sick a little easier

than other people, My health is excellent, etc.”) and energy/fatigue levels (e.g. “During the past four weeks, did you feel worn out?”), as well as a prompt to gauge individual understanding of health progression (“Compared to one year ago, how would you rate your health in general now?”) (J. Ware, Snoww, MA, & BG, 1993). To score the completed form, the eight categories are scaled and calculated into numbers from 0 to 100, with a lower value indicating greater disability (0 correlates to maximum disability, 100 to no disability present). The survey is widely used within clinical research and health policy evaluations, as well as general population surveys (J. E. Ware & Sherbourne, 1992).

- Pain Catastrophizing Scale (PCS): Developed by Michael JL Sullivan, Ph.D., the pain catastrophizing scale is a series of 13 questions to allow research of catastrophizing behaviors related to pain experiences. The data can be translated into three subsets: rumination (“I can’t stop thinking about how much it hurts”), magnification (“I worry that something serious may happen”) and helplessness (There is nothing I can do to reduce the intensity of the pain”) (Sullivan, 2009). Incorporated within the A2A baseline survey, participants are asked to rate the degree to which they experienced each thought or feeling on a five-point scale from 0 (not at all) to 4 (all the time). The questions are divided between the PCS categories and the summation of each is used to determine significance. PCS scores allow providers to gain insight into the coping methods their patient utilizes for chronic pain. Understanding the manner in which an individual

responds to a pain condition can aid in treatment development and long-term care planning.

- Medical History: In addition to information regarding symptoms related to the menstrual cycle and pain perception, the baseline survey provides a thorough review of individual medical history. This includes questions regarding acne/pimples, bodily hair growth, and prior surgical encounters. Of interest to this study, the medical history section of the baseline survey also reviews possible comorbid conditions including asthma, diabetes, thyroid disorders, fibromyalgia, migraines, gastroesophageal reflux disease, cancer and mood disorders, which are separated into questions specific to anxiety disorder, depression/mood disorder, eating disorder, and attention deficit disorder. When prompted with “Have you ever been told by a doctor that you have any of these conditions?”, a positive confirmation then prompts the participant to detail age of diagnosis and any medications they have taken for more than three months within the past year. Review of medical history information provided the framework for further investigation into the presence of mood disorders within the study cohort.

Pain Sensitivity Questionnaire

- Participants were asked to complete the Pain Sensitivity Questionnaire (PSQ), a series of seventeen situational questions to be answered using a numerical scale. All questions present a scenario that may elicit pain and ask the participant to rate their perceived pain level from 0 to 10 (0 = not painful at all, 10 = most severe

pain imaginable). Of the seventeen questions, three are not considered painful by healthy subjects (Azimi & Benzel, 2016). Only whole-number answers are recorded. Individuals are asked to focus on pain perception and avoid feelings of fear or aversion to proposed situations. Examples of PSQ scenarios include “Imagine you have grazed your knee falling off your bicycle”. First developed in German, the PSQ has been adapted to the English language with similar success (Sellers, Ruscheweyh, Kelley, Ness, & Vetter, 2013). The questions are scored into two categories: PSQ-minor, which takes the average response of seven questions deemed to elicit minor levels of pain in a healthy individual, and PSQ moderate, which does the same for seven questions presumed to generate moderate pain levels (Ruscheweyh et al., 2012). PSQ score analysis allows further understanding of perceived pain levels compared to healthy baseline values.

Quantitative Sensory Testing

- For the physical portion of the protocol, patients participated in a version of Quantitative Sensory Testing (QST), a noninvasive assessment of sensory detection and threshold (Cornelissen et al., 2014). Developed to assess large and small nerve fiber function related to pain in the research setting, QST can determine thresholds of thermal, mechanical touch and vibration across the body. Pain sensation from mechanical, thermal or deep pressure can also be assessed at various body sites (Cornelissen et al., 2014). In addition to recording sensation and pain thresholds, QST can also be used to measure temporal summation, or the sensory detection by a single stimulus. For this test, one QST measure is

repeatedly applied to the same test site and sensation or pain detection is recorded. Temporal summation can detect the presence of a wind-up phenomenon, where a repeated application of the same stimuli produced increased levels of sensation. In this study, mechanical detection and mechanical and pressure thresholds as well as wind-up temporal summation QST was used. All study parameters were first applied to the control site (deltoid muscle for mechanical, thumbnail for pressure) before abdominal administration to the four quadrants (upper left, upper right, lower left, lower right). The study protocol included the following:

- Touch and sharpness sensations were determined using Von Frey hairs. Developed in 1896 by Maximilian von Frey, these hairs are a type of aesthesiometer designed to detect light touch sensation and are comprised of plastic filaments of increasing diameter (Fruhstorfer, Gross, & Selbmann, 2001). For each level of sensation, the participant was asked to rate any pain on a numerical scale from 0 to 10.
 - Touch sensation level was determined by the repeated application of Von Frey hairs in increasing diameter until sensory detection was confirmed via repeated blind stimulation.
 - Sharpness threshold was recorded using the same process, with the participant indicating the sensation of a ‘sharp prick’ or ‘a needle’ through multiple (2 out of 3 trials) blind administrations.
 - Temporal summation was determined using the Von Frey hair producing the sharpness threshold through repeated application,

with the pain rating recorded for each. The presence of wind-up phenomenon served as a surrogate for central sensitization.

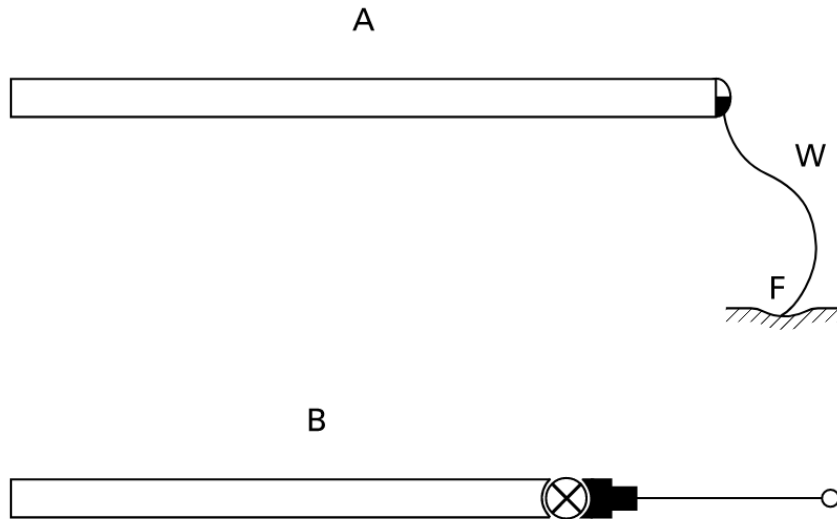


Figure 5: Von Frey Filaments. (A) Represents original Von Frey drawing where W represents the filament and F identifies dermal site of application. (B) Represents an illuminated filament. (W) refers to the filament, (F) to the dermal test site. Fruhstorfer, H., Gross, W., & Selbmann, O. (2001). von Frey hairs: new materials for a new design. *European Journal of Pain (London, England)*, 5(3), 341–342.

- Pressure sensation was determined using an algometer on the thumbnail (control site) and abdominal quadrants. Participants were asked to indicate when they experienced discomfort, at which point the applied pressure level was recorded. Each site was tested three times, after which an average recording was calculated.

Medical Chart Review

- In addition to information collected from the baseline questionnaires, medical chart review was performed on all participants with the purpose of confirming the diagnosis of anxiety, depression or other mood disorder. The reasoning for further review of patient medical history was due to the self-reporting nature of the A2A baseline survey and possibility for mis- or underreporting mood disorder diagnoses. Charts were reviewed to collect presence of mood disorder diagnosis and, if present, type of disorder, number of current medications (with current defined as the date of or most recent clinic appointment prior to participation in the study), types of medication if applicable, and family history of endometriosis with detail to specific family member with disease.

RESULTS

In total, the cohort contains 48 participants ranging in age from 14 to 22 (mean=17.65, SD=1.91), who are all residents of the greater Boston area and enrolled either in middle school, high school or undergraduate coursework. The age of first menarche ranged from 10 to 15 years old (mean=11.51, SD=1.30) and stage of endometriosis ranged from I to II based on the ASRM classification scale performed by Dr. Marc Laufer at BCH. Dr. Laufer performed all diagnostic laparoscopic procedures and initiated similar treatment protocols to all participants. The participation in QST was between 19 and 1685 days (M=4.61 years, SD=1.33 years) from the date of first surgery. Comparing date of surgery to time of QST participation, the reported pain at QST was related to days since surgery and showed lower pain levels correlated to a higher number of days since surgery. Further demographic information about the participants is provided in Table 1.

Table 1: Demographic Information

	Frequency <i>(Range, Mean, [Standard Deviation])</i>	
<i>Age of Participant on DOS</i>	14-22, 17.65, [1.91]	
<i>Age of First Menstrual Period</i>	10-15, 11.51, [1.30]	
<i>Days between DOS and QST</i>	19-1,685, 651.08, [486.08]	
	Frequency	Percent
<i>Race of Participant (n=45)</i>		
White	36	75.0
“Spanish/Hispanic/Latina”	3	6.3
Black/African American	2	4.2
Other	4	8.3
<i>Current Education Status (n=44)</i>		
Middle School	2	4.2
High School	34	70.8
College	8	16.8
<i>Current work status (n=42)</i>		
Full time student	36	75
Working in paid job as employee	3	6.3
Unable to work	1	2.1
Other	2	4.2

Of the 48 participants, 20 had confirmed mood disorder diagnoses (+MD) of either anxiety or depression treated with prescription medication at time of study participation. Of the 20 confirmed diagnoses, 12 self-reported their diagnosis on the A2A baseline questionnaire and 8 were collected during a cohort-wide medical chart review. All 20 +MD subjects presented with anxiety and 12 were receiving additional treatment for depression. Treatment ranged from one (n=14) to three (n=1) prescription medications and a total of 9 different medications were used within the cohort, the details of which are listed in Table 2. The most common form of pharmacotherapy was a selective serotonin reuptake inhibitor (SSRI) (n=18), followed by a serotonin norepinephrine reuptake inhibitor (SNRI) (n=2).

Table 2: Types of Prescription Medications for the Treatment of Anxiety and Depression within the Cohort

Type of Medication	Generic (Brand)	# of Participants
SSRI	Fluoxetine (Prozac)	9
SSRI	Citalopram (Celexa)	4
SSRI	Sertraline (Zoloft)	3
Benzodiazepine	Clonazepam (Klonopin)	3
SNRI	Venlafaxine (Effexor XR)	2
Benzodiazepine	Lorazepam (Ativan)	2
SSRI	Escitalopram (Lexapro)	1

Quantitative Sensory Testing Analysis

Aim 1a: To determine the occurrence of wind-up temporal summation, which is a surrogate for central sensitization, in an adolescent and young adult cohort of patients with surgically confirmed endometriosis.

The cohort was evaluated for the presence of wind-up, considered a surrogate of central sensitization, using the temporal summation and sharp prick pain scores recorded during QST. Using a calculated ratio between average temporal summation and mechanical stimulation threshold pain ratings, a score above 0.33 (or 33%) indicates the presence of central sensitization through wind-up phenomenon. Of the 48 participants, 23 received scores above 0.33 and were determined to have presented with central sensitization (47.9%). 25 participants (52.1%) were determined to not have wind-up, and therefore did not have central sensitization. Within the group with central sensitization

(+CS), 18 subjects presented with wind-up of the lower abdomen, 15 in the upper abdomen, 21 in the abdomen only, three in the deltoid only and nine presented with systemic presence of wind-up (lower and upper abdomen, deltoid). Detailed analysis is found in Table 2. Bivariate Pearson correlations were used to assess relationships between QST measures and central sensitization. Wind-up of the upper abdomen was positively correlated with lower abdomen wind-up ($r=0.60$, $p<0.01$). Average pressure ratings from the finger positively correlated to average pressure ratings of the upper abdomen ($r=0.60$, $p<0.01$) and lower abdomen ($r=0.59$, $p<0.01$). Average pressure ratings of the upper and lower abdomen were also significantly correlated ($r=0.88$, $p<0.01$).

Table 3: Correlations between QST Variables

	Central Sensitization	Wind-up in the upper abdomen	Wind-up in the lower abdomen	Average pressure sensation and pain in the upper abdomen	Average pressure sensation and pain in the upper abdomen	Average pressure sensation and pain of the finger
Central Sensitization	1	.613**	.808**	.008	.009	.068
	48	.000	.000	.956	.952	.648
		48	48	48	48	48
Wind-up in the upper abdomen	.613**	1	.592**	-.097	-.161	-.123
	.000	.000	.000	.514	.274	.405
	48	48	48	48	48	48
Wind-up in the lower abdomen	.808**	.592**	1	.008	-.032	.125
	.000	.000	.000	.955	.831	.397
	48	48	48	48	48	48
Average pressure sensation and pain in the upper abdomen	.008	-.097	.008	1	.876**	.601**
	.956	.514	.955	.000	.000	.000
	48	48	48	48	48	48
Average pressure sensation and pain in the lower abdomen	.009	-.161	-.032	.876**	1	.586**
	.952	.274	.831	.000	.000	.000
	48	48	48	48	48	48
Average pressure sensation and pain of the finger	.068	-.123	.125	.601**	.586**	1
	.648	.405	.397	.000	.000	.000
	48	48	48	48	48	48

** . Correlation is significant at the 0.01 level (2-tailed).

Paired t-tests for wind-up measures showed a significant difference between pressure ratings of the finger (M=33.7, SD=19.05) and average pressure ratings of the upper abdomen (M=13.33, SD=5.16), $T(48)=8.57$, $p<0.001$; as well as with lower abdomen pressure (M=13.65, SD= 6.33), $T(48)=8.59$, $p<0.001$, indicating that the pressure thresholds in the abdomen area for this sample were lower compared to the finger.

Aim 1b: To determine if the presence of mood disorders is related to pain sensitivity and if it is greater in patients with central sensitization.

To examine the relationship between central sensitization and mood disorder diagnosis within the cohort, a cross tabulation of the data was performed. Of the 20 subjects with confirmed mood disorder diagnoses (+MD), 12 were within the +CS group (60%) and 8 identified as -CS (40%). As part of the +CS group, +MD subjects represented 57.1% of all cases of wind-up. For depression, cross tabulation between the 12 identified subjects and central sensitization showed equal distribution across the +/-CS groups with six subjects in each (50%). Participants with depression represented 28.6% of the +CS group. Of note, all participants with diagnoses of depression also presented with confirmed anxiety disorder. Neither the relationship between anxiety and central sensitization or between depression and central sensitization was statistically significant.

Table 4: Anxiety and Depression as related to Central Sensitization

			+CS or -CS	
			No	Yes
Anxiety	No	Count	17	9
		% within +CS or -CS	68.0%	42.9%
	Yes	Count	8	12
		% within +CS or -CS	32.0%	57.1%
Total	Count	25	21	
			+CS or -CS	
			No	Yes
Depression	No	Count	19	15
		% within +CS or -CS	76.0%	71.4%
	Yes	Count	6	6
		% within +CS or -CS	24.0%	28.6%
Total	Count	25	21	

The relationship between anxiety and wind-up presentation was examined. Using one-way analysis of variance (ANOVA), a positive correlation between anxiety and wind-up in the abdomen ($M=0.33$, $p<0.05$) was found.

Table 5: Correlations between +MD and Central Sensitization

	Central Sensitization	Anxiety	Depression	Windup in the abdomen (upper or lower)
Central Sensitization	1	.253	.052	.835**
		.090	.732	.000
	48	46	46	48
Anxiety	.253	1	.677**	.333*
	.090		.000	.024
	46	46	46	46
Depression	.052	.677**	1	.105
	.732	.000		.488
	46	46	46	46
Wind-up in the abdomen (lower or upper)	.835**	.333*	.105	1
	.000	.024	.488	
	48	46	46	48

** . Correlation is significant at the 0.01 level (2-tailed).

* . Correlation is significant at the 0.05 level (2-tailed).

Emotional Wellbeing Within the Cohort

Aim 2: To compare quality of life and pre-surgical pain catastrophizing measures in patients with endometriosis to determine whether the presence of central sensitization and/or mood disorders impacts quality of life and pain catastrophizing.

Using one-way analysis of variance (ANOVA), a positive correlation between anxiety and finger pressure pain ($M=0.32$, $p<0.05$), was found. For wind-up scores, a positive correlation was found between deltoid wind-up and pre-operative pain scores ($M=0.30$, $p<0.05$), rumination ($M=0.42$, $p<0.05$) and pain catastrophizing (total score) ($M=0.37$, $p<0.05$).

One-way ANOVA was also used to identify potential differences between the +CS and -CS groups in regards to pre-surgical pain catastrophizing. Pain Catastrophizing

Scale measures of helplessness, rumination and magnification were reviewed for significance. Although there were no significant differences between the two groups on pre-surgical pain and pre-surgical pain catastrophizing, the +CS group showed clinically significant rumination ($M=11.17$, $SD=6.41$) and the entire sample demonstrated clinically significant feelings of helplessness ($M=13.26$, $SD=6.41$) (Sullivan, 2007).

Participants were asked to rate recent pain experiences during QST administration. Worst pain the last six months was negatively correlated to average pressure ratings of the finger ($r=-0.57$, $p<0.01$). Pre-operative pain scores were recorded from A2A surgical forms and medical chart review. Pre-operative pain was significantly correlated with PCS subscales of rumination ($r=0.48$, $p<0.01$), magnification ($r=0.44$, $p<0.01$), and PCS total score ($r=0.44$, $p<0.01$).

One-way ANOVA was used to compare the PSQ total and subscale scores of the sample to published healthy control means. There was found to be a significant difference between PSQ minor sub-score for the sample ($M=2.9$, $SD=1.37$), and the healthy control ($M=2.5$, $SD=+/-1.1$); $t(48)=2.09$, $p=0.04$, indicating that the present sample is bothered more by minor sensory stimuli.

Significant correlations were found when comparing pre-operative pain and pain catastrophizing measures from PCS across the cohort as a whole. Pre-operative pain was significantly correlated to PCS total score ($r=0.44$, $p<0.01$), magnification ($r=0.44$, $p<0.01$) and rumination ($r=0.48$, $p<0.01$). No significance was found between pre-operative pain and helplessness within the cohort.

Table 6: Correlations (r) between Anxiety Dimensions and Functional Disability

Correlations

	Pre-surgical pain score	PCS - rumination	PCS - magnification	PCS - helplessness	PCS total score
Pre-surgical pain score	1	.480**	.438**	.336	.444**
	47	.004	.009	.052	.008
		34	34	34	34
PCS - rumination	.480**	1	.674**	.817**	.926**
	.004		.000	.000	.000
	34	34	34	34	34
PCS - magnification	.438**	.674**	1	.684**	.820**
	.009	.000		.000	.000
	34	34	34	34	34
PCS - helplessness	.336	.817**	.684**	1	.952**
	.052	.000	.000		.000
	34	34	34	34	34
PCS Total Score	.444**	.926**	.820**	.952**	1
	.008	.000	.000	.000	
	34	34	34	34	34

** . Correlation is significant at the 0.01 level (2-tailed).

Table 7: Correlations between QST Measures, Pre-surgical Pain and Pain Catastrophizing Scale Components

	Central Sensitization	Wind-up in the deltoid	Average pressure sensation and pain of the finger	Pre-surgical pain score	"In the last six months, what was your worst pain?"	PCS - rumination	PCS total score
Central Sensitization	1	.669**	.068	.034	.116	.246	.227
	48	.000	.648	.820	.590	.161	.197
		48	48	47	24	34	34
Wind-up in the deltoid	.669**	1	-.221	.303	.206	.423	.370
	.000		.131	.038	.334	.013	.031
	48	48	48	47	24	34	34
Average pressure sensation and pain of the finger	.068	-.221	1	.008	-.566**	-.202	-.103
	.648	.131		.960	.004	.251	.562
	48	48	48	47	24	34	34
Pre-surgical pain score	.034	.303	.008	1	-.139	.480**	.444**
	.820	.038	.960		.528	.004	.008
	47	47	47	47	23	34	34
"In the last six months, what was your worst pain?"	.116	.206	-.566**	-.139	1	-.127	-.191
	.590	.334	.004	.528		.639	.479
	24	24	24	23	24	16	16
PCS - rumination	.246	.423	-.202	.480**	-.127	1	.926**
	.161	.013	.251	.004	.639		.000
	34	34	34	34	16	34	34
PCS total score	.227	.370	-.103	.444**	-.191	.926**	1
	.197	.031	.562	.008	.479	.000	
	34	34	34	34	16	34	34

** . Correlation is significant at the 0.01 level (2-tailed).

* . Correlation is significant at the 0.05 level (2-tailed).

DISCUSSION

This study seeks to identify the relationship comorbid factors play in the development of chronic pelvic pain with endometriosis. The results of the reviewed variables show no significant relationship between the presence of anxiety or depression with central sensitization or pain catastrophizing. Although the data contradicted the proposed hypotheses there is a need for great consideration as to why the results presented opposite to what was expected. Post-hoc analysis of data variables presented several points for discussion when considering the results, study limitations and future directions.

Hypothesis 1: Participants with diagnosed mood disorders will have greater pain sensitivity, lower pain thresholds, and a higher occurrence of central sensitization compared to participants without mood disorders.

The cohort was moderately split between participants with and without central sensitization. Within the measures of QST, the correlation between average pressure sensation and pain scores of the finger, upper abdomen and lower abdomen imply positive relationships between test sites regarding deep pressure pain sensation. Lower and upper abdomen wind-up threshold correlation shows even pain distribution within the sample, rather than quadrant-specific pain sensitivity, which is in line with the development of CS and is to be expected (Melzack & Katz, 2012). Compared to pilot data for this sample from 2017, the rate of wind-up phenomenon has increased from 24% to 47.9% within the cohort (Resad, 2017). One point of note from the QST data was the

presence of wind-up phenomenon only at the deltoid control site for three participants. This data presentation was determined to fall into the category of central sensitization even though it was not detected at the abdominal test sites and suggests central generalization of sensory input that is not correlated with assumed anatomical regions for CS with CPP. This spread of pain sensitivity specific to central sensitization was demonstrated through the use of nerve blocks to isolate pain sensation, however the mechanism and duration of migrating sensation has been debated (Woolf, 2011). Continued research as the sample grows will allow further understanding of this phenomenon.

The only significant relationship found between +MD and central sensitization was between anxiety and wind-up threshold of the abdomen, highlighting a relationship between anxiety and heightened mechanical touch sensitivity within the cohort. No other significant relationship was found between mood disorder diagnosis and presence of central sensitization. Occurrence of +MD was almost equally split between +CS and –CS groups (see Table 3). As the results go against the proposed hypothesis, several theories have been proposed for the reasoning behind the equal distribution and lack of significance within the +MD group including the extensive use of pharmacotherapeutics within the sample.

Pharmacotherapy for Comorbid Symptoms

In this cohort, all participants with a diagnosed mood disorder were being treated by a prescription medication, however, only 10% of the +MD subgroup was treated with

an SNRI (versus SSRI). To date, there is not enough data to support the use of SNRIs versus SSRIs in cases of adolescent major depressive disorder and, as of 2016, SNRI medications are not recommended by the FDA as first line therapy (Garland, Kutcher, Virani, & Elbe, 2016). Given this information, it is understandable why the majority of +MD study subjects are being treated with SSRIs. However, when looking at mental health as a comorbid condition to endometriosis, especially in cases including chronic pelvic pain, only using symptoms of anxiety and depression when determining pharmacotherapeutic regimen does not adequately address the overall symptom presentation. Consideration should be taken for secondary effects of available medications that could alleviate primary symptoms of endometriosis, including pelvic pain.

The standard treatment for depression and some anxiety in adolescent and adult populations, SSRI and SNRI drugs have also been trialed in chronic pain populations for the purpose of reducing pain symptoms. Although results for SSRI use for chronic pain in adolescents have been inconclusive (Patetsos & Horjales-Araujo, 2016), the positive effects of SNRI medications for pain reduction have been shown in studies on adult subjects (Obata, 2017). SNRIs are able to dampen pain signaling through the inhibition of norepinephrine reuptake in the dorsal horn of the spinal cord. By binding to α_2 -adrenergic receptors and preventing a cellular signaling cascade, SNRIs hyperpolarize the cell membranes and prevent the release of excitatory neurotransmitters from primary afferent fibers (Obata, 2017). Of note, although this inhibitory mechanism is effective against

allodynia and hyperalgesia, it does not provide adequate pain reduction for noxious stimuli (Obata, 2017).

It is also possible to use SSRIs for the reduction of side effects brought on by GnRHAs in cases of severe endometriosis, and should be considered as adolescents mature and utilize GnRHa therapy as adult patients. Further research should be performed to look at the relationship between endometriosis, chronic pelvic pain, mood disorders and the efficacy of SSRI and SNRI medications on the symptoms presenting from these comorbid conditions.

Hypothesis 2: The presence of anxiety, depression and central sensitization in patients with endometriosis will be higher in those demonstrating pre-surgical pain catastrophizing and will negatively relate to quality of life measures.

Scores collected from pre-surgical forms and visits to the BCH clinic showed a positive correlation to PCS total score, as well as the subsets of rumination and magnification. This describes the sample as one with high levels of pain and catastrophizing behaviors before surgical intervention for endometriosis. This relationship is anticipated in cases of chronic pain (Miller & Kaiser, 2018). Pre-surgical pain scores also correlated to wind-up phenomenon in the arm, which although unexpected, proposes a heightened awareness of input by the nervous system only at the start of QST due to the failure of correlation by abdominal wind-up variables. More in line with expected norms, average pressure sensation and pain scores for the arm were positively correlated with pain scores in response to the question ‘In the past six months,

what was your worst pain?’ which was asked at the time of QST participation. This relationship indicates a decreased pain threshold and increased pain awareness within the cohort.

PCS total score and the subset measures of helplessness and rumination were significantly correlated to wind-up variables and highlight a strong relationship between the presence of central sensitization and pain catastrophizing. This relationship can be explained by the adaptation by the nervous system during development of CS to generalize incoming stimuli, which is similar to the thought generalization that occurs during catastrophizing behavior (Sullivan, 2009). The tendency to overreact and remain at a heightened level of sensitivity to incoming stimuli – whether that may be mechanical or cognitive – is found in both phenomena.

Represented by the PCS helplessness and PSQ minor variables, clinically significant levels of pain catastrophizing were identified throughout the sample. Both categories produced clinically significant values for both +CS and –CS groups, indicating the universal presence of helplessness and increased pain sensitivity to situations deemed slightly painful compared to healthy controls and standard clinical values. These results highlight the impact endometriosis and comorbid conditions have on the adolescent population and propose the investigation into the source of helplessness and pain sensitivity. One potential source, parental support, has been highlighted as a factor in child functioning in cases of chronic pain, and endometriosis being a hereditary disease adds an additional factor to this relationship.

Endometriosis: A Hereditary Disease

For cases of chronic pain within the adolescent population, parent involvement plays a definitive role in treatment outcomes and recovery, and chronic pain conditions frequent impact the entire family unit (Sieberg, Williams, & Simons, 2011). Parents are likely to have an emotional response to their child's pain, which can impact their own psychological response to the condition and influence child functioning (Sieberg et al., 2011). Ineffective responses by parents to their child's pain, including reassurance, solicitous, and protective parenting behaviors, increase the likelihood of adverse outcomes in both clinical pain (Claar, Simons, & Logan, 2008) and experimentally induced pain populations (Walker et al., 2006). When looking specifically at parent distress in relation to child functional disability, Sieberg et al. determined that all examined variables (helplessness, parent depression, anxiety, and catastrophizing) were significantly correlated to child functional disability (Sieberg et al., 2011). This study showed a relationship between parental variables and child functional disability, which was partially mediated by parent protectiveness. Although parent protectiveness in response to child pain is common, their actions do not correlate with improved pain outcomes (Connelly et al., 2010).

As a hereditary condition, the growth of endometrial lesions can be predicted as adolescents reach puberty and experience similar pain symptoms to older relatives with the disease. The unique relationship between generations of women within a family in regards to pathological symptoms and treatment could easily magnify the results of parent protective responses. In addition to presenting the common parental responses of

protectiveness, involved family members with a history of endometriosis share personal experiences with similar pain symptoms, which could lead to higher pain responses by girls with a family history of endometriosis as parent protectiveness plays an even larger role.

Limitations

Limitations of the study should be addressed. Most noticeable is the small sample size of which this data was collected from. Participants were recruited at follow-up outpatient appointments where time constraints due to travel or other appointments were often the barrier between consent and refusal. Visit length was frequently longer than scheduled, but while this prevented patients from participating, the reason for the appointment is the primary concern and should not be neglected for research purposes. Expanding the recruitment locations to outpatient clinics both in Boston and Lexington, Massachusetts allowed more opportunity for patient enrollment. Further participation incentive through parking validation was implemented in February 2018.

Additionally, it is important to note that over the course of 48 patients, five different members of the BPP lab performed QST. While all members were fully trained on the study protocol, the possibility of personal bias when presenting the protocol should be considered. Training continuity and familiarization with the study protocol in the future may reduce the impact this limitation has on data collection. Of note, for the three patients presenting with deltoid-only wind-up, different test administrators were cited for each, all at different stages of protocol experience, suggesting no connection between

unexpected CS results and administrator error. To date, any evidence within the data set of operator error has not presented as so.

Another possible limitation of this study concerns participant doubt with protocol progression. The use of Von Frey filaments requires the participant to state when they feel the sensation of a “needle or sharp prick” as filament diameter is increased from their level of sensation. Participants are instructed prior to Von Frey application to alert the researcher if any pain is detected. The wording, along with the concept of identifying a strong feeling just prior to pain sensation, may elicit premature declaration of a “needle or sharp prick” sensation. Temporal summation of the filament determined to illicit this sensation commonly produced statements of doubt from participants, bringing to light the possibility of suggested sensation misinterpretation. This could prevent the detection of central sensitization by using a Von Frey filament too small in diameter to propagate the appropriate pain threshold response. Further education on the purpose of the filaments could alleviate this possible limitation.

Participants may also report low levels of pain during QST due to comparison of pain experienced from endometriosis and CPP symptoms. In an effort to demonstrate the severity of cyclic pain symptoms, subjects may underreport pain sensation produced during QST. The collection of recent pain ratings prior to QST administration (“What is your current pain rating?”, “What was your worst pain rating in the past three weeks?”, etc.) may help validate reports of severe pain symptoms by participants, however these scores were not collected for the first 20 subjects in the cohort.

The time between day of surgery (DOS) and date of QST administration ranged from 19 to 1685 days (mean = 651 days). This suggests a few implications within the data set. First, for women who underwent QST within a month of surgery, lower pain scores may have been reported due to lack of a complete menstrual cycle post-lesion resection. As endometrial lesions develop with rising estrogen levels, the lack of a complete cycle may prevent any new lesion growth. Without further disease progression and current presence of pelvic pain symptoms, QST data may not be able to detect presence of wind-up at time of participation. A review of pain scores from QST versus DOS could aid in understanding the development of pain symptoms for patients with short DOS/QST timeframes. Second, the mean number of days from DOS to date of QST was about 21 months. Extensive time between DOS and QST allows for disease development and progression that is not tracked by this study. Participants may have received additional procedures to remove endometrial lesions, which would weaken the relationship between DOS and QST pain scores. Working with an adolescent population, developmental gains are likely to occur between completion of the baseline questionnaire and date of QST. As the cohort matures, their comprehension of the disease and pain management, including pain catastrophizing, evolves. Follow up surveys with similar prompts could show changes in participant responses.

Future Directions

The next step for this study is to establish a control sample for the comparison of QST values. The control group will undergo thermal imaging of the pelvic region in addition to current study measures (QST and PSQ).

Currently participants are recruited from the Women's Health Study, which will terminate enrollment in June 2018. Although not all A2A participants are also enrolled in this study, the completion of patient recruitment for A2A decreases administrative support for further enrollment towards this ongoing project. Efforts to recruit from other studies in the future are ongoing. The continuation of A2A after enrollment completion will be in the form of follow up surveys and longitudinal tracking of participants. The addition of post-hoc surveys to further understand the mental health profile of all A2A participants would allow better understanding of pain development in patients with these comorbid conditions.

The current data review was limited by the validity and detail of mood disorder diagnosis, as all information came from self-reported baseline questionnaires and medical chart review. Follow up surveys for study participants including specific measures of mental health would more accurately define the cohort. This would also allow researchers to screen all participants, not just those with records of diagnoses of anxiety and depression, for a range of mental health disorders. Possible tools include the Children's Depression Inventory (CDI) or the Hospital Anxiety and Depression Scale (HADS) for depression, and the Youth Anxiety Measure (YAM-5) or Kutcher Generalized Social Anxiety Scale for Adolescents (K-GSAS-A) for the presence of anxiety.

As an ongoing study, further investigation of the relationship between endometriosis, CPP, mental health, pre-surgical pain catastrophizing and the development of CS within the adolescent population are encouraged. The collection of additional participant data from A2A longitudinal progression analysis, subsequent surgical documentation and participation in thermal QST measures will all positively contribute to the success of this study. The effect of mental health and pain catastrophizing on adolescents with endometriosis is clearly connected to the presence of CPP and CS development. Defining these relationships and developing strategies for early detection and intervention can improve quality of life for those affected and should be taken into consideration for future research.

REFERENCES

- American Society for Reproductive Medicine. (1997). Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertility and Sterility*, 67(5), 817–821.
- Azimi, P., & Benzel, E. C. (2016). Cut-Off Value for Pain Sensitivity Questionnaire in Predicting Surgical Success in Patients with Lumbar Disc Herniation. *PLOS ONE*, 11(8), e0160541.
- Baranowski, A. P. (2009). Chronic pelvic pain. *Best Practice & Research Clinical Gastroenterology*, 23(4), 593–610.
- Brawn, J., Morotti, M., Zondervan, K. T., Becker, C. M., & Vincent, K. (2014). Central changes associated with chronic pelvic pain and endometriosis. *Human Reproduction Update*, 20(5), 737–747.
- Bridge, J. A., Iyengar, S., Salary, C. B., Barbe, R. P., Birmaher, B., Pincus, H. A., ... Brent, D. A. (2007). Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA*, 297(15), 1683–1696.
- Cavaggioni, G., Lia, C., Resta, S., Antonielli, T., Benedetti Panici, P., Megiorni, F., & Porpora, M. G. (2014). Are Mood and Anxiety Disorders and Alexithymia Associated with Endometriosis? A Preliminary Study. *BioMed Research International*, 2014.
- Claar, R. L., Simons, L. E., & Logan, D. E. (2008). Parental response to children's pain: the moderating impact of children's emotional distress on symptoms and disability. *Pain*, 138(1), 172–179.
- Connelly, M., Anthony, K. K., Sarniak, R., Bromberg, M. H., Gil, K. M., & Schanberg, L. E. (2010). Parent pain responses as predictors of daily activities and mood in children with juvenile idiopathic arthritis: the utility of electronic diaries. *Journal of Pain and Symptom Management*, 39(3), 579–590.
- Cornelissen, L., Donado, C., Kim, J., Chiel, L., Zurakowski, D., Logan, D. E., ... Berde, C. B. (2014). Pain hypersensitivity in juvenile idiopathic arthritis: a quantitative sensory testing study. *Pediatric Rheumatology*, 12(1), 39.
- Cruz-Almeida, Y., & Fillingim, R. B. (2014). Can quantitative sensory testing move us closer to mechanism-based pain management? *Pain Medicine (Malden, Mass.)*, 15(1), 61–72.

- DiVasta, A. D., Vitonis, A. F., Laufer, M. R., & Missmer, S. A. (2017). Spectrum of symptoms in women diagnosed with endometriosis during adolescence vs adulthood. *American Journal of Obstetrics and Gynecology*.
- Doyle, J. O., Missmer, S. A., & Laufer, M. R. (2009). The Effect of Combined Surgical-Medical Intervention on the Progression of Endometriosis in an Adolescent and Young Adult Population. *Journal of Pediatric and Adolescent Gynecology*, 22(4), 257–263.
- Friedl, F., Riedl, D., Fessler, S., Wildt, L., Walter, M., Richter, R., ... Böttcher, B. (2015). Impact of endometriosis on quality of life, anxiety, and depression: an Austrian perspective. *Archives of Gynecology and Obstetrics*, 292(6), 1393–1399.
- Fruhstorfer, H., Gross, W., & Selbmann, O. (2001). von Frey hairs: new materials for a new design. *European Journal of Pain (London, England)*, 5(3), 341–342.
- Jane Garland, E., Kutcher, S., Virani, A., & Elbe, D. (2016). Update on the Use of SSRIs and SNRIs with Children and Adolescents in Clinical Practice. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, 25(1), 4–10.
- Janssen, E. B., Rijkers, A. C. M., Hoppenbrouwers, K., Meuleman, C., & D'Hooghe, T. M. (2013). Prevalence of endometriosis diagnosed by laparoscopy in adolescents with dysmenorrhea or chronic pelvic pain: a systematic review. *Human Reproduction Update*, 19(5), 570–582.
- Kapoor, S., Thorn, B. E., Bandy, O., & Clements, K. L. (2015). Pain referents used to respond to the pain catastrophizing scale. *European Journal of Pain (London, England)*, 19(3), 400–407.
- Laganà, A. S., La Rosa, V. L., Rapisarda, A. M. C., Valenti, G., Sapia, F., Chiofalo, B., ... Vitale, S. G. (2017). Anxiety and depression in patients with endometriosis: impact and management challenges. *International Journal of Women's Health*, 9, 323–330.
- Laufer, M. R., Goitein, L., Bush, M., Cramer, D. W., & Emans, S. J. (1997). Prevalence of endometriosis in adolescent girls with chronic pelvic pain not responding to conventional therapy. *Journal of Pediatric and Adolescent Gynecology*, 10(4), 199–202.
- Laufer, Marc R, Sanfilippo, J., & Rose, G. (2003). Adolescent Endometriosis: Diagnosis and Treatment Approaches. *Journal of Pediatric and Adolescent Gynecology*, 16(3, Supplement), S3–S11.

- Matalliotakis, M., Goulielmos, G. N., Matalliotaki, C., Trivli, A., Matalliotakis, I., & Arici, A. (2017). Endometriosis in Adolescent and Young Girls: Report on a Series of 55 Cases. *Journal of Pediatric and Adolescent Gynecology*, *30*(5), 568–570.
- Melzack, R., & Katz, J. (2012). Pain. *Wiley Interdisciplinary Reviews: Cognitive Science*, *4*(1), 1–15.
- Milingos, S., Protopapas, A., Kallipolitis, G., Drakakis, P., Loutradis, D., Liapi, A., & Antsaklis, A. (2006). Endometriosis in patients with chronic pelvic pain: is staging predictive of the efficacy of laparoscopic surgery in pain relief? *Gynecological and Obstetric Investigation*, *62*(1), 48–54.
- Miller, R. M., & Kaiser, R. S. (2018). Psychological Characteristics of Chronic Pain: a Review of Current Evidence and Assessment Tools to Enhance Treatment. *Current Pain and Headache Reports*, *22*(3), 22.
- Obata, H. (2017). Analgesic Mechanisms of Antidepressants for Neuropathic Pain. *International Journal of Molecular Sciences*, *18*(11).
- Patetsos, E., & Horjales-Araujo, E. (2016). Treating Chronic Pain with SSRIs: What Do We Know? *Pain Research & Management*, *2016*.
- Pereira, F. G., França, M. H., de Paiva, M. C. A., Andrade, L. H., & Viana, M. C. (2017). Prevalence and clinical profile of chronic pain and its association with mental disorders. *Revista de Saúde Pública*, *51*.
- Pielech, M., Ryan, M., Logan, D., Kaczynski, K., White, M. T., & Simons, L. E. (2014). Pain catastrophizing in children with chronic pain and their parents: Proposed clinical reference points and re-examination of the PCS measure. *Pain*, *155*(11), 2360–2367.
- Pope, C. J., Sharma, V., Sharma, S., & Mazmanian, D. (2015). A Systematic Review of the Association Between Psychiatric Disturbances and Endometriosis. *Journal of Obstetrics and Gynaecology Canada*, *37*(11), 1006–1015.
- Resad, S. (2017). Examining associations between psychophysical functioning and pain in young women with endometriosis and chronic pelvic pain: a pilot study. Retrieved from <https://open.bu.edu/handle/2144/23845>
- Rolke, R., Baron, R., Maier, C., Tölle, T. R., Treede, R.-D., Beyer, A., ... Wasserka, B. (2006). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain*, *123*(3), 231–243.

- Roman, H., Bourdel, N., Rigaud, J., Delavierre, D., Labat, J.-J., & Sibert, L. (2010). Endométriose et douleurs pelvipérinéales chroniques. *Progrès En Urologie*, 20(12), 1010–1018.
- Ruscheweyh, R., Verneuer, B., Dany, K., Marziniak, M., Wolowski, A., Colak-Ekici, R., ... Knecht, S. (2012). Validation of the pain sensitivity questionnaire in chronic pain patients. *Pain*, 153(6), 1210–1218.
- Saridoğan, E. (2015). Endometriosis in Teenagers. *Women's Health*, 11(5), 705–709.
- Sellers, A. B., Ruscheweyh, R., Kelley, B. J., Ness, T. J., & Vetter, T. R. (2013). Validation of the English language pain sensitivity questionnaire. *Regional Anesthesia and Pain Medicine*, 38(6), 508–514.
- Shin, J. H., & Howard, F. M. (2011). Management of Chronic Pelvic Pain. *Current Pain and Headache Reports*, 15(5), 377.
- Sieberg, C. B., Williams, S., & Simons, L. E. (2011). Do parent protective responses mediate the relation between parent distress and child functional disability among children with chronic pain? *Journal of Pediatric Psychology*, 36(9), 1043–1051.
- Smorgick, N., Marsh, C. A., As-Sanie, S., Smith, Y. R., & Quint, E. H. (2013). Prevalence of Pain Syndromes, Mood Conditions, and Asthma in Adolescents and Young Women with Endometriosis. *Journal of Pediatric and Adolescent Gynecology*, 26(3), 171–175.
- Steege, J. F., & Siedhoff, M. T. (2014). Chronic pelvic pain. *Obstetrics and Gynecology*, 124(3), 616–629.
- Stein, S. L. (2013). Chronic pelvic pain. *Gastroenterology Clinics of North America*, 42(4), 785–800.
- Stuparich, M. A., Donnellan, N. M., & Sanfilippo, J. S. (2017). Endometriosis in the Adolescent Patient. *Seminars in Reproductive Medicine*, 35(01), 102–109.
- Sullivan, M. J. (2009). *The Pain Catastrophizing Scale*. Montreal, Canada.
- van Aken, M. A. W., Oosterman, J. M., van Rijn, C. M., Ferdek, M. A., Ruigt, G. S. F., Peeters, B. W. M. M., ... Nap, A. W. (2017). Pain cognition versus pain intensity in patients with endometriosis: toward personalized treatment. *Fertility and Sterility*, 108(4), 679–686.
- Vancini, R. L., Rayes, A. B. R., Lira, C. A. B. de, Sarro, K. J., Andrade, M. S., Vancini, R. L., ... Andrade, M. S. (2017). Pilates and aerobic training improve levels of

- depression, anxiety and quality of life in overweight and obese individuals. *Arquivos de Neuro-Psiquiatria*, 75(12), 850–857.
- Vercellini, P., Viganò, P., Somigliana, E., & Fedele, L. (2014). Endometriosis: pathogenesis and treatment. *Nature Reviews Endocrinology*, 10(5), 261–275.
- Vitale, S. G., Rosa, V. L. L., Rapisarda, A. M. C., & Laganà, A. S. (2017). Impact of endometriosis on quality of life and psychological well-being. *Journal of Psychosomatic Obstetrics & Gynecology*, 38(4), 317–319.
- Walker, L. S., Williams, S. E., Smith, C. A., Garber, J., Van Slyke, D. A., & Lipani, T. A. (2006). Parent attention versus distraction: impact on symptom complaints by children with and without chronic functional abdominal pain. *Pain*, 122(1–2), 43–52.
- Ware, J. E., & Sherbourne, C. D. (1992). The MOS 36-Item Short-Form Health Survey (SF-36) [Product Page]. Retrieved March 20, 2018, from https://www.rand.org/pubs/external_publications/EP19920602.html
- Ware, J., Snoww, K., MA, K., & BG, G. (1993). *SF36 Health Survey: Manual and Interpretation Guide* (Vol. 30).
- Warnock, J., Bundren, J. C., & Morris, D. (1998). Sertraline in the Treatment of Depression Associated with Gonadotropin-Releasing Hormone Agonist Therapy. *Biological Psychiatry*, 43, 464–465.
- Woolf, C. J., & Salter, M. W. (2000). Neuronal plasticity: increasing the gain in pain. *Science (New York, N.Y.)*, 288(5472), 1765–1769.
- Woolf, Clifford J. (2007). Central Sensitization Uncovering the Relation between Pain and Plasticity. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, 106(4), 864–867.
- Woolf, C. J. (2011). Central sensitization: Implications for the diagnosis and treatment of pain. *Pain*, 152(3 Suppl), S2–15.
- Young, K., Fisher, J., & Kirkman, M. (2017). Clinicians' perceptions of women's experiences of endometriosis and of psychosocial care for endometriosis. *The Australian & New Zealand Journal of Obstetrics & Gynaecology*, 57(1), 87–92.
- Zito, G., Luppi, S., Giolo, E., Martinelli, M., Venturin, I., Di Lorenzo, G., & Ricci, G. (2014). Medical Treatments for Endometriosis-Associated Pelvic Pain. *BioMed Research International*, 2014.

CURRICULUM VITAE

