

2017

Examining associations between psychophysical functioning and pain in young women with endometriosis and chronic pelvic pain: a pilot study

<https://hdl.handle.net/2144/23845>

"Downloaded from OpenBU. Boston University's institutional repository."

BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**EXAMINING ASSOCIATIONS BETWEEN PSYCHOPHYSICAL
FUNCTIONING AND PAIN IN YOUNG WOMEN WITH
ENDOMETRIOSIS AND CHRONIC PELVIC PAIN: A PILOT STUDY**

by

SEHAR RESAD

B.A., University of Chicago, 2015

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

2017

Approved by

First Reader

Jean-Jacques R. Soghomonian, Ph.D.
Associate Professor of Anatomy and Neurobiology

Second Reader

Christine B. Sieberg, Ph.D., Ed.M., M.A.
Attending Psychologist
Department of Anesthesia – Boston Children’s Hospital
Assistant Professor
Department of Psychiatry-Harvard Medical School
Director
Biobehavioral Pediatric Pain Lab- Boston Children’s Hospital

ACKNOWLEDGMENTS

I wish to acknowledge those who have played an integral role in my academic pursuits thus far, and have provided me with the necessary support to help in the completion of this thesis.

To my loving family and friends: Your unwavering, unfaltering support and patience with me have not gone unnoticed or unappreciated. Your constant encouragement and belief in me has kept me striving for greater and greater pursuits.

To Christine Sieberg and the entire Biobehavioral Pediatric Pain Lab: I could not have asked for a more encouraging group of mentors and colleagues. The autonomy I was allowed by Dr. Sieberg instilled in me a belief that I am capable of taking on any project, yet the constant support from the lab as a whole ensured I never had to do so alone. The amount I was able to learn in such a short time speaks remarkably to the wonderful mentor Dr. Sieberg is, and the incredible atmosphere she has created at the BPP. Also, a special thank you to Cindy Wong, Dr. Navil Sethna, and the Women's Health Study for their particular help in the completion of this thesis.

**EXAMING ASSOCIATIONS BETWEEN PSYCHOPHYSICAL FUNCTIONING
AND PAIN IN YOUNG WOMEN WITH ENDOMETRIOSIS AND CHRONIC
PELVIC PAIN: A PILOT STUDY**

SEHAR RESAD

ABSTRACT

Objectives: This study aims to explore the relationships between preoperative psychosocial factors in relation to postoperative chronic pelvic pain (CPP) in adolescents and young women with endometriosis, which is a significant public health concern. As a pilot sample, there is large need to present preliminary data exploring the biopsychosocial correlates and possible predictors of central sensitization and CPP, which remains non-existent in the realm of adolescents and young adults with CPP secondary to endometriosis.

Methods: Eligible candidates included patients 12-22 years old who were diagnosed with CPP after laparoscopic confirmation of endometriosis. 25 successfully enrolled subjects had pre-surgical information obtained from baseline surveys and underwent a postoperative sensory protocol to assess mechanical allodynia, pressure pain sensitivity, central sensitization, and a self-report measure of pain sensitivity. Correlation calculations were conducted between pre-surgical factors (pain intensity, pain catastrophizing (PCS), and quality-of-life (from SF-36)) and post-surgical factors (pain and sensitivity thresholds as measured by QST and the PSQ) in the subject population as a whole, and in two population subgroups: those exhibiting central sensitization and those who are not. One-way ANOVA calculations and one sample t-tests were conducted to

compare differences between cohorts and between abdominal and control sites for various study parameters.

Results: 6 of 25 (24%) subjects experienced a wind-up phenomenon during the temporal summation for pain test, serving as a surrogate for central sensitization. The differences in study parameters that this group (+CS) exhibited in comparison to the –CS group, failed to reach significance in all study parameters. Both cohorts exhibited positive correlations between pre-operative disability due to bodily pain (SF-36) and sensitivity of the abdomen, as well as negative correlations between disability due to bodily pain and pressure pain thresholds of the abdomen. The +CS cohort also exhibited a negative correlation between disability due to bodily pain and pinprick pain scores, a positive correlation between role limitations due to physical health (SF-36) and sensitivity of the abdomen, and a positive correlation between pain catastrophizing and sensitivity of the abdomen. As a whole, the subject population had significantly higher levels of catastrophizing than published means. In all cohorts, pressure pain thresholds of the abdomen were significantly lower than the control values, and PSQ-minor scores were significantly higher than published means.

Conclusions: Results suggest the importance of pre-operative pain and psychosocial functioning on pain outcomes, particularly when considering subjects presenting with central sensitization, in young women with CPP secondary to endometriosis. The results indicate the need for a larger sample as well as established control values to further explore the relationships between these variables.

TABLE OF CONTENTS

TITLE.....	i
COPYRIGHT PAGE.....	ii
READER APPROVAL PAGE.....	iii
ACKNOWLEDGMENTS	iv
ABSTRACT.....	v
TABLE OF CONTENTS.....	vii
LIST OF TABLES	ix
LIST OF FIGURES	x
LIST OF ABBREVIATIONS.....	xi
INTRODUCTION	1
Endometriosis Presentation, Diagnosis, and Treatment	2
Chronic Pelvic Pain Secondary to Endometriosis	8
Biopsychosocial Contributions of Pain and Central Sensitization	11
Assessing Pain Intensity and Sensitivity	17
Specific Aims and Objectives	20
METHODS	22
Participants	23
Measures	23

<i>Baseline Survey</i>	23
<i>Pain Intensity</i>	26
<i>Quantitative Sensory Testing (QST)</i>	26
<i>Pain Sensitivity Questionnaire (PSQ)</i>	29
RESULTS	30
Aim 1	31
Aim 2	33
Aim 3.	39
DISCUSSION.....	44
Future Directions	52
Limitations	54
REFERENCES	56
CURRICULUM VITAE.....	63

LIST OF TABLES

Table	Title	Page
1	Staging of endometriosis and lesions in relation to pain	7
2	Participant data on pain experiences	30
3	Psychophysical parameter means in population subsets	32
4	Correlations between pre-operative health factors and post-operative QST and PSQ in entire sample	35
5	Correlations between pre-operative health factors and post-operative QST and PSQ in –CS subset	36
6	Correlations between pre-operative health factors and post-operative QST and PSQ in +CS subset	37
7	QST and PSQ means	38
8	Correlations between PCS and post-operative QST and PSQ in entire sample	40
9	Correlations between PCS and post-operative QST and PSQ in -CS subset	41
10	Correlations between PCS and post-operative QST and PSQ in +CS subset	42
11	Frequency of participants with clinically relevant catastrophizing	43

LIST OF FIGURES

Figure	Title	Page
1	Protocol for evaluation and treatment of adolescent pelvic pain and endometriosis	5
2	Possible description of the relationship between endometriosis and CPP	9
3	Biopsychosocial approach to pain	12
4	Four anatomical quadrants of the abdomen	28

LIST OF ABBREVIATIONS

BCE.....	Boston Center for Endometriosis
BCH	Boston Children’s Hospital
BWH	Brigham and Women’s Hospital
CPP	Chronic Pelvic Pain
NSAIDs.....	Nonsteroidal Anti-Inflammatory Drugs
PCS	Pain Catastrophizing Scale
PSQ	Pain Sensitivity Questionnaire
QST.....	Quantitative Sensory Testing
SF-36.....	36-Item Short Form Health Survey
WHS.....	Women’s Health Study

INTRODUCTION

Endometriosis is a chronic, progressive gynecologic disease affecting 10-15% of women of reproductive age (Carey, Martin, Siedhoff, Bair, & As-Sanie, 2014), and is defined pathologically as the presence of viable endometrial tissue outside of the normal anatomic location (American College of Obstetricians and Gynecologists, 2005). Subsequently, the presence of this extrauterine tissue, and the consequent inflammation and fibrosis, can lead to persistent inflammatory pain, infertility, and significant disruption of quality of life (American College of Obstetricians and Gynecologists, 2005). Though endometriosis has historically been thought of as a disease affecting adult women only after many years of menstruation, many studies have described endometriosis in adolescents. Presentation of the disease in adolescents has been found to range as early as prior to menarche, to one and five months after menarche (Goldstein, deCholnoky, Leventhal, & Emans, 1979; Laufer, 2000; Yamamoto et al., 1997).

Due to decades of research, focus on adolescent endometriosis has moved from non-recognition and case reports, to diagnosis after menarche, to recognition and diagnosis even before menarche (Batt & Mitwally, 2003). The incidence of endometriosis in adolescents and young women is unknown, even though many diagnosed adult women report that their symptoms began when they were significantly younger (Smorgick, Marsh, As-Sanie, Smith, & Quint, 2013). Despite increasing awareness; delayed diagnosis, high rates of misdiagnosis, and delayed treatment are issues faced in young women with endometriosis. It is crucial that an adequate diagnosis is made, as adolescent

endometriosis is a debilitating chronic disease that negatively impacts participation in daily activities, including but not limited to school and emotional well-being (Youngster, Laufer, & Divasta, 2013).

Endometriosis is often the underlying cause of chronic pelvic pain (CPP), which is generally defined as noncyclic pain at or below the umbilicus of at least 3 to 6 months' duration that interferes with daily activities (Powell, 2014). Studies have shown that 25-38% of young women with chronic pelvic pain have endometriosis (Kontoravdis et al., 1999; Vercellini et al., 1989) and up to nearly 75% of young women with pelvic pain who do not respond to nonsteroidal anti-inflammatory drugs (NSAIDs) or hormonal therapy for dysmenorrhea have endometriosis (Doyle, Missmer, & Laufer, 2009). Over time, CPP becomes unresponsive to standard medical and surgical therapies due to excessive pain sensitivity known as central sensitization (Giamberardino, Tana, & Costantini, 2014). Systematic evaluation of pain sensitivity of painful and non-painful body sites and how they interact with psychosocial functioning could be important for monitoring clinical progress of CPP and response to treatment. Not only has this association not been adequately investigated in adult humans, but also no studies exist looking at adolescents and young adults with CPP secondary to endometriosis, and thus is a focus of this thesis.

Endometriosis Presentation, Diagnosis, and Treatment

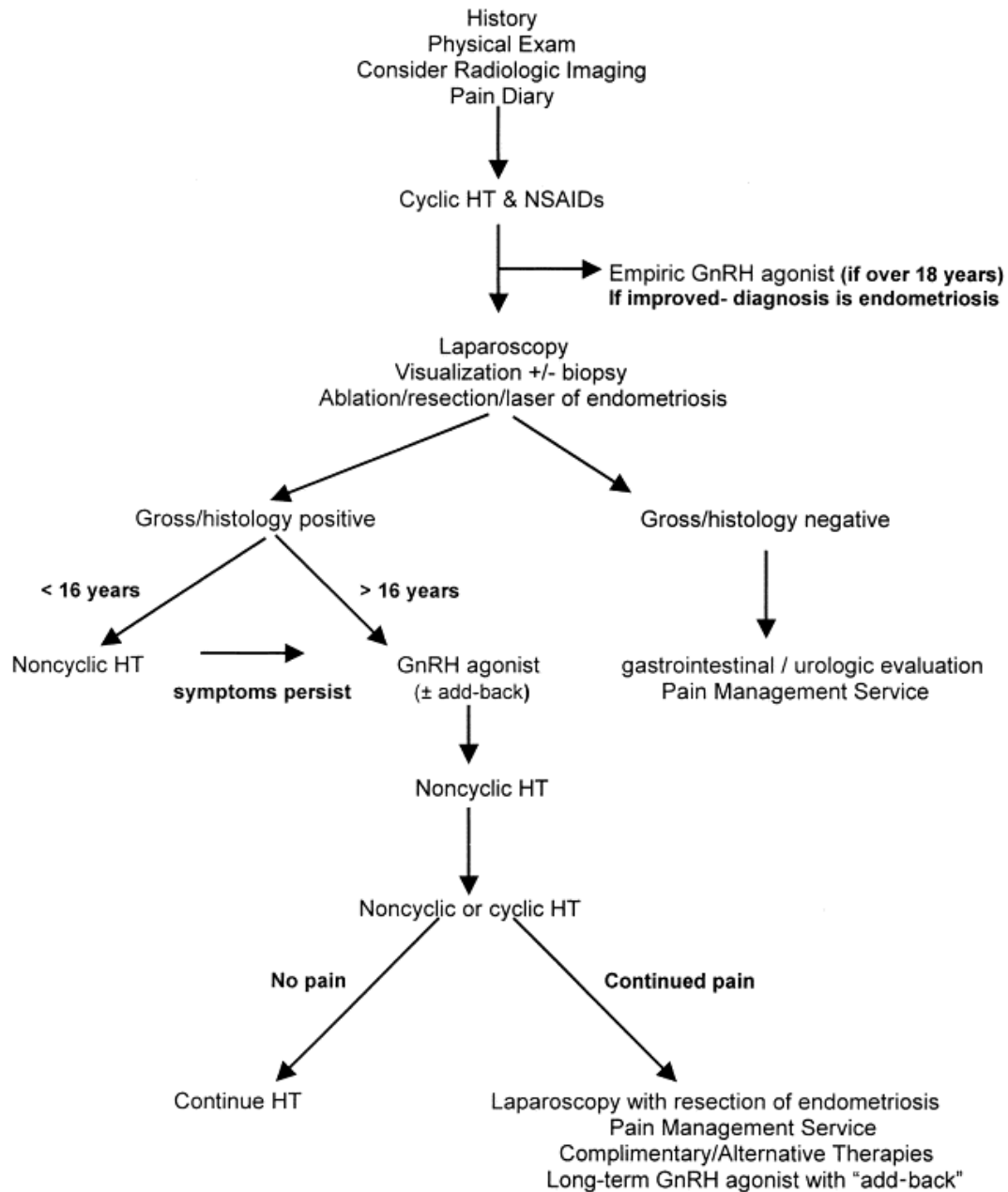
Dysmenorrhea is a common symptom of adolescents and affects up to 50% of young women, with 15% experiencing severe forms (Mavrelou & Saridogan, 2013).

Adolescents usually experience painful periods due to primary dysmenorrhea, which begins 6-12 months after menarche once ovulatory cycles are established and in which there is no pelvic pathology. Primary dysmenorrhea usually responds well to treatment with NSAIDs and/or oral contraceptive pills. However, many adolescents describe pain symptoms that start beyond one year after menarche and persist despite treatment with the mentioned medication (Laufer, Sanfilippo, & Rose, 2003; Saridoğan, 2015). It is these patients who appear to be experiencing secondary dysmenorrhea, for which endometriosis is often the underlying pathology.

Diagnosis of endometriosis in young women has proven to be quite difficult. Data from the Endometriosis Association indicate that patients whose symptoms began before the age of 15 saw an average of 4.2 doctors compared with an average of 2.64 doctors for patients whose symptoms began between the ages of 30 and 34. Adolescents are more likely to present with combined acyclical and cyclic pain (62.5%) or acyclical pain alone (28.1%), unlike adult women with endometriosis who are more likely to experience cyclical pain only, which only 9.4% of adolescents with endometriosis experience (American College of Obstetricians and Gynecologists, 2005; Laufer et al., 2003; Saridoğan, 2015). Additionally, adolescents found to have endometriosis frequently display comorbid bowel and bladder symptoms as well (Laufer, Goitein, Bush, Cramer, & Emans, 1997).

While research efforts are focusing on the development of noninvasive diagnostic modalities and treatments, laparoscopic surgery remains the standard method to confirm the diagnosis of endometriosis. After a long preoperative trial period consisting of

extensive evaluation and combination hormonal and NSAID treatment for dysmenorrhea, laparoscopy is recommended to both diagnose and remove any ectopic tissue (American College of Obstetricians and Gynecologists, 2005; Youngster et al., 2013). The multistep process that is required for differential diagnosis results in an average of 9.28 years from the onset of symptoms to the diagnosis of endometriosis (Ballweg, 2003). An algorithm for diagnosis and therapy is provided in Figure 1.



NSAIDs – Nonsteroidal anti-inflammatory drugs; HT – Hormonal Therapy (oral contraceptive pills, estrogen/progestin patch, estrogen/progestin vaginal ring, norethindrone acetate, medroxyprogesterone acetate); GnRH – gonadotropin-releasing hormone; “ add-back” – estrogen + progestin or norethindrone acetate alone

Figure 1. Protocol for evaluation and treatment of adolescent pelvic pain and endometriosis. Standard model proposed by Bandera CA, Brown LR, Laufer MR. Adolescents and endometriosis. Clin Consult Obstet Gynecol 1995;7:206, modified and adapted from American College of Obstetricians and Gynecologists (2005).

At the time of laparoscopy, the endometriosis is staged according to the American Society of Reproductive Medicine Classification in order to facilitate follow-up and comparison if future surgery is performed. Most adolescents present with Stage I or Stage II disease characterized by isolated lesions and no significant adhesions (Stage I) or superficial lesions less than 5 cm in aggregate without significant adhesions (Stage II). Endometriosis found in young women tends to present with high abundance of red and clear lesions as opposed to the “powder-burn” black lesions seen commonly in adults (Laufer et al., 2003). For post-operative counseling, it is important to keep in mind that the severity of symptoms has not been found to correlate with stage, perhaps since it has been suggested that clear and red lesions are the more painful lesions of endometriosis (see Table 1) (Laufer et al., 2003). Laparoscopic removal alone is not sufficient treatment for endometriosis and must be supplemented with medical therapy such as hormonal therapy, and/or GnRH antagonists. With surgery alone, symptoms have been shown to return in approximately 50% of adult women within 1 year (Gambone, Mittman, Munro, Scialli, & Winkel, 2002; Sutton, Ewen, Whitelaw, & Haines, 1994).

Table 1: Staging of endometriosis and lesions in relation to pain. Adapted from Marc R. Laufer et al. (2003)

		Association with Pain
Stage of Disease	Stage I	40%
	Stage II	24%
	Stage III	24%
	Stage IV	12%
Type of Lesion	Clear	76%
	Red	84%
	White	44%
	Black	22%

Though most patients respond well to these treatments and have decreased pain; a subset of patients present with ongoing pain despite surgical and medical therapies. Nearly 30% of women report no improvement in pain after laparoscopy. Even when patients do express improvement initially, many of them eventually have recurrence of symptoms. Further, the degree of short-term pain improvement among the patients varies and pain symptoms recur despite the absence of pathological disease or new lesions (Abbott, Hawe, Hunter, Holmes, Finn, & Gary, 2004). Over time the CPP becomes unresponsive to standard medical and surgical interventions. In the Pain Treatment Service at Boston Children’s Hospital (BCH), the institution where the current data was collected, nearly 50 new patient evaluations are conducted per year on young women with CPP.

Chronic Pelvic Pain Secondary to Endometriosis

The American College of Obstetricians and Gynecologists (ACOG) defines chronic pelvic pain as pain of six or more months' duration that is situated in the abdomen, groin, or lower back and interferes with daily activities. The differential diagnosis of CPP in the adolescent has significant overlap with the causes in adults, but evaluation in the adolescent involves several additional challenges, including parent-child-provider reluctance to do a gynecologic history or examination and issues with patient-provider confidentiality, as the parent or guardian is generally involved in the visit and medical decision making (Powell, 2014). CPP is known to have both gynecologic and non-gynecologic causes, but is extremely prevalent for gynecologic patients with nearly 25% of all patients being affected (Giamberardino et al., 2014). Among adolescents seen at pediatric pain management clinics, endometriosis is a frequent culprit, affecting 45% to 70% of adolescents with CPP (Laufer et al., 1997).

Despite its high prevalence and negative effects, little is known about the pathophysiology underlying the development and persistence of chronic pelvic pain despite surgical and medical intervention. Of note is the fact that the presence and severity of pelvic pathology does not correlate with symptom burden (Vercellini et al., 1989). Standard medical and surgical therapies targeting endometriosis lesions are not consistently effective and pain frequently recurs even without visible disease at repeat laparoscopy (Figure 2) (As-Sanie, Harris, Harte, Tu, Neshewat, & Clauw, 2013; Hurd, 1998). Many adolescent with pelvic pain from endometriosis maintain normal activity, but those seen at pain clinics tend to represent a subgroup of patients who, despite

aggressive medical and surgical therapy, continue to experience significant pain and disability such as: missed school, decreased leisurely activities, decreased accomplishment of tasks, and decreased general well-being, often leading to symptoms such as anxiety and depression (Greco, 2003; Simis et al., 2015).

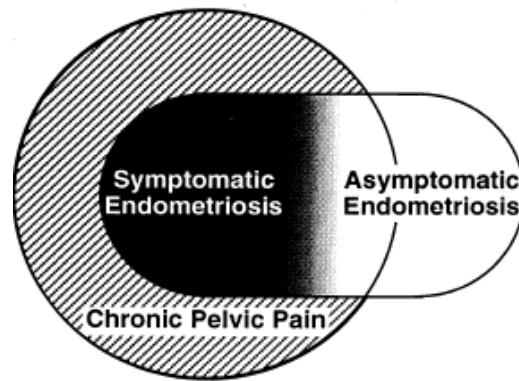


Figure 2. Possible description of the relationship between endometriosis and CPP. In women with chronic pelvic pain and endometriosis, the majority of patients do not experience CPP when the endometriosis is asymptomatic. However, some patients present with asymptomatic endometriosis that is still incidental to the CPP. Adapted from Hurd (1998).

Many studies support that a significant cause for the development of CPP is central sensitization. While the heightened sensitivity of peripheral pain receptors following a local trauma or infection, such as that caused by endometriosis, usually resolves with time, in CPP this hypersensitivity is sustained and amplified by an extensive central neural network that includes various subsets of neural networks and results in neuropathic pain (Simis et al., 2015; Whitaker et al., 2016). Most pelvic organs, as well as somatic pelvic tissues to which the pain is referred, share at least part of their central sensory projection. This may trigger the phenomena of cross-sensitization and central sensitization (Giamberardino et al., 2014).

Animal models support the theory that a process of central sensitization likely results in CPP in this population via a viscera-visceral referred hyperalgesia. This refers to a process in which increased input to the nervous system from one visceral domain can sensitize neurons that receive convergent input from another visceral domain. (Berkley, Cason, Jacobs, Bradshaw, & Wood, 2001). Because almost all spinal neurons that receive visceral input also receive somatosensory input from the muscle and skin through a process known as viscerosomatic convergence, precise localization and discrimination of sensory information is hindered (Aredo, Heyrana, Karp, Shah, & Stratton, 2017). In the rat, it is confirmed that input from the uterus to the spinal cord is mainly by way of hypogastric nerve at the thoracic level, and that from the cervix is by way of both the pelvic and hypogastric nerves; suggesting possible routes of convergence and referred pain (Berkley, Robbins, & Sato, 1993). Neurons within both sets of segments have demonstrated to respond convergently to stimulation of the uterus, colon, and vagina and significant interactions exist between these two separated sets of caudal spinal segments (Berkley et al., 1993; Wall, Hubscher, & Berkley, 1993). These studies support the theory that sensitized afferents directly innervate regions surrounding the endometrial growths resulting in a central sensitization within the caudal spinal cord that is then referred to other visceral domains, including the vaginal canal (Berkley et al., 2001).

While these animal models are interesting and provide insight into the potential role of central sensitization in CPP associated with endometriosis, there has been virtually no research conducted among humans. One study found that peripheral pressure-pain thresholds were lower in women with endometriosis and CPP and in

women with CPP without endometriosis, when compared to both women with endometriosis and no CPP and pain-free women (As-Sanie et al., 2013). Another study proposed modulating central nervous system activity in chronic pain states by non-invasive brain stimulation in the form of transcranial direct current stimulation (tDCS). This study, performed by Simis et al., (2015), found that patients with CPP had significant increases in pain thresholds after active tDCS suggesting further presence of neuromodulatory involvement in CPP (Simis et al., 2015). Despite these findings, no research of this type has been conducted with the specific aims at understanding these relationships in young women with endometriosis and CPP.

Biopsychosocial Contributions of Pain and Central Sensitization

Many factors have been implicated in the generation of persistent postoperative pain such as: preoperative pain intensity, pain sensitivity, age, biological sex, psychological status, and hormonal status (Jarrell & Arendt-Nielsen, 2013). Thus the development of central sensitization and concurrent CPP is believed to be multifactorial, with incidence in only a subset of all patients with endometriosis. The biopsychosocial model has largely been a focus in pain research, with many tertiary pain rehabilitation facilities basing their assessment and treatment methods on its emphasis on the integration of the physical, psychological, and social aspects of one's life (Celedon, Amari, Ward, Prestwich, & Slifer, 2014). Because studies have shown that up to 55% of women with CPP have no obvious underlying pathology (Whitaker et al., 2016), it is important to consider the breadth of biopsychosocial factors that could contribute to the

multifactorial etiology of CPP secondary to endometriosis (Figure 3). As with other chronic pain conditions, there is evidence to suggest that a multidisciplinary approach to the assessment and treatment of chronic pelvic pain is effective in improving patients' response to therapy and in their overall outcome (Greco, 2003).

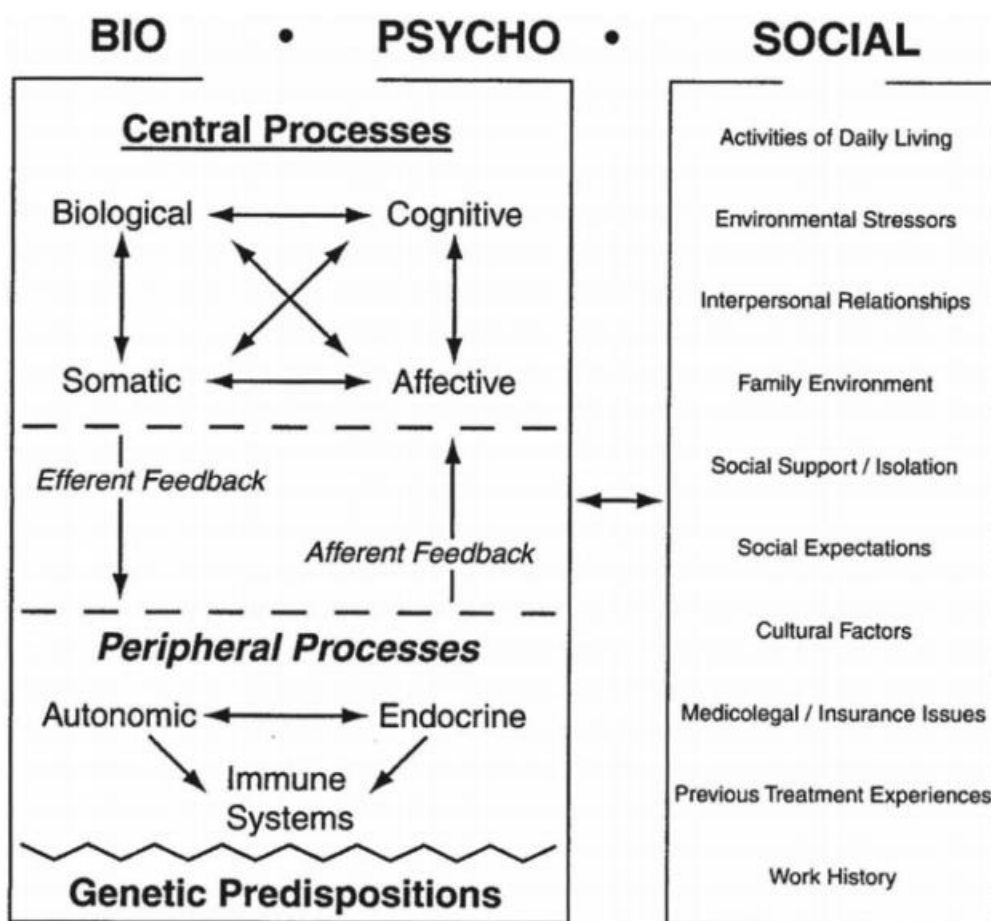


Figure 3: Biopsychosocial approach to pain. A conceptual model of the biopsychosocial interactive processes involved in health and illness. Adapted from Gatchel, Peng, Peters, Fuchs, & Turk, (2007)

Biologically, pain sensitivity, or thresholds to deeming stimuli as painful, are likely in part due to genetic factors (Phillips & Clauw, 2011). This can be supported by

studies showing that children with chronic pain often have a family history of pain, including specific studies on headaches, migraines, and abdominal pain (Boey & Goh, 2001; Evans et al., 2008). Further, a twin study done by Nielsen and colleagues (2008) found that pain sensitivity in response to cold and heat pain was correlated between fraternal and identical twins. High preoperative pain sensitivity (low pain thresholds) has been found to parallel an increased risk to chronic pain (Nielsen et al., 2008) and these pain thresholds can be further reduced in response to visceral disease such as endometriosis. The pain from the initial endometriosis can evoke changes in the spinal segments that innervate the affected visceral organs, leading to increased painful neuronal signals directed to the spinal cord and resulting in continuous increased pain and larger areas of referred pain (Jarrell & Arendt-Nielsen, 2013). Further, the resulting peripheral pain stimulus has been shown to be related to the release of various cytokines (glutamate, prostaglandins, bradykinin) that are known activators of nociceptors, causing increased pain sensation (Jarrell & Arendt-Nielsen, 2013; Moshiree, Zhou, Price, & Verne, 2006; Vergnolle, 2008). It is extremely important to explore and assess these relationships in adolescents with endometriosis, as they present differently than adults.

Psychophysiological factors are also believed to play a role in the development of central sensitization. Activation of the stress-response network has been shown to lower pain thresholds in both animals and humans, and high levels of anxiety are consistently related to higher pain sensitivity (McAllister, 2012). Many studies have shown a prior history of anxiety, physical and psychological trauma, and depression to be significantly predictive of the onset of chronic pain later in life (McLean, Clauw, Abelson, &

Liberzon, 2005; Talbot et al., 2009). This indirect evidence suggests that pre-existing dysregulation of the nervous system and the development of central sensitization may be the underlying substrate for the high susceptibility to chronic pain development, but this possibility needs to be explored more specifically in the context of chronic pelvic pain.

When considering dysregulation of the nervous system due to high psychological distress, catastrophization is of particular interest as a strong driving force (Carey et al., 2014; Martin et al., 2011). Catastrophization is a negative cognitive and emotional coping mechanism in response to pain in which the emotional distress associated with feeling that one's own pain is the worst possible and unlikely to improve (Sullivan, Bishop, & Pivik, 1995). Catastrophizing has emerged as an important determining factor in pain-related outcomes and is consistently associated with higher pain levels (Carey et al., 2014; Martin et al., 2011). Martin et al., (2011) studied the effects of catastrophizing as a predictor of persistent pain particularly in women with endometriosis and found catastrophizing to be a significant predictor of pain at 1 year post-laparoscopy. However, they also found other pre-existing biopsychosocial factors that assume a key role in pain-related outcomes suggesting that endometriosis-related CPP may be more complex in some patients.

The exact mechanism through which catastrophizing affects pain outcomes is not completely understood, but hypotheses have suggested it leads to biological effects supporting the development of central sensitization. It has been hypothesized that endogenous pain-inhibitory pathways are disrupted by the emotional and cognitive changes that characterize catastrophizing (Sullivan et al., 2001). This would lead to

higher levels of pain sensation in response to painful stimuli. Further, catastrophizing has been shown to be associated with increased neural activity in pain-processing regions of the brain (Martin et al., 2011). Both findings support the notion of central sensitization and other involvements particular to pain perception. Particular to endometriosis as an inflammatory process, positive associations between catastrophizing and inflammatory cytokines have been found in other similar disease processes such as arthritis and rheumatic disease, and could be relevant to the study of pain in endometriosis (Edwards et al., 2008; Yin et al., 2005). Exposure to painful stimuli leads to an upregulation of inflammatory cytokines, and higher levels of catastrophizing were related to greater pain-related increases in levels of inflammatory cytokines suggesting that catastrophization leads to increased responsiveness to painful stimuli and might represent an important mechanism in shaping long-term pain outcomes (Edwards et al., 2008). In particular, Interleukin-6 (an inflammatory cytokine) is directly known to induce muscle and joint heightened sensitivity to pain.

The onset of pain, for example due to the onset of endometriosis, is often followed by the development of numerous psychosocial disorders such as depression, fear-avoidance, anxiety, and other stressors (Smorgick et al., 2013). Young women with chronic pelvic pain can experience associated depression, anxiety, and fear that may perpetuate and intensify their overall pain experience (Greco, 2003; Smorgick et al., 2013). It is known that psychosocial variables contribute significantly to postoperative outcome measures (Carey et al., 2014), but long-term predictors of pain outcomes following laparoscopy for endometriosis have not been adequately described in adults nor

even explored in the adolescent patient population. The stress of these responses to the initial pain can further exacerbate the reactivity of the nervous system, leading to a heightened predisposition to the development of central sensitization. (Diatchenko, Nackley, Slade, Fillingim, & Maixner, 2006).

Previous studies in adult women diagnosed with endometriosis found that preoperative pain intensity was correlated with pain intensity following laparoscopic removal of the endometrial tissue (Coccia, Rizzello, Palagiano, & Scarselli, 2011), depression, and somatic awareness (Walker, Hopman, Harrison, Tripp, & VanDenKerkhof, 2012). Minimal research has been done on the contribution of biopsychosocial factors on young women with endometriosis and CPP, but a study done by Smorgick et al., (2013) found depression and anxiety to be highly prevalent in adolescents diagnosed with endometriosis, paralleling previous findings in adult women. It is clinically important to assess for the presence of mood conditions because if untreated, they can have negative effects on patients' ability to cope with their pain and carry out their daily function, and further contribute to their pain experience (Poleshuck et al., 2010).

The clinical implications of these psychological associations have relevance to the pre- and postoperative counseling of patients with CPP. Elucidating the biopsychosocial factors that contribute to CPP in postsurgical young women with endometriosis and CPP could allow for preoperative identification of patients with high-risk features and for early intervention to address surgical expectation with regards to the treatment of pain. This thesis aims to further explore the relationships between these biopsychosocial

factors and psychophysical functioning variables with pain outcomes, particularly in young women with chronic pelvic pain secondary to endometriosis, in the hopes to elucidate any predisposing factors for at-risk adolescents.

Assessing Pain Intensity and Sensitivity

Assessing the amount of pain a patient experiences is difficult due to the subjective nature of pain. Without a baseline level of pain sensitivity, is it difficult to assign a comparable value to pain using a numerical rating scale of “0”, no pain, to “10”, worst pain imaginable. Persons with high sensitivity would rate the same painful stimulus at a higher numerical rating than someone with a low sensitivity. The German Research Network on Neuropathic Pain developed Quantitative Sensory Testing (QST) in order to understand the mechanisms underlying the sensations patients with neuropathic pain feel. In their efforts, they were able to obtain a full somatosensory phenotype for a patient, including primary afferents, cutaneous and deep pain, and peripheral and central sensitization (Rolke et al., 2006).

The QST protocol consists of seven different tests that are used to measure thirteen parameters grouped into the following: (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, (4) mechanical pain sensitivity including thresholds for pinprick and blunt pressure, (5) stimulus/response-functions for pinprick sensitivity, (6) dynamic mechanical allodynia, and (7) pain summation to repetitive pinprick stimuli (wind-up like pain) (Rolke et al.,

2006). Detection thresholds ask the participant to state when they feel anything in general, such as a change in temperature when assessing thermal detection. Mechanical detection thresholds are assessed using von Frey's hairs (nylon filaments of increasing thickness), and are reached when the subject can perceive the tactile stimulus on their skin. Pain thresholds assess at which point the stimulus becomes painful or no longer bearable, for example due to extreme hot or cold, sharp pricking from a von Frey's hairs, or intense pressure using a pressure gauge device. This protocol was found to be a novel method encompassing all somatosensory modalities assessing the functioning of different nerve fibers and of central pathways (Blankenburg et al., 2010).

QST has been used in research settings and is considered an appropriate tool for diagnosing, assessing, and monitoring sensory neuropathies and determining pain sensitivity in adults with pain disorders (Backonja et al., 2013; Blankenburg et al., 2010). Rolke et al. (2006) determined the reference values of the face, hand, and foot in gender- and age-matched healthy adults. However, QST has not been utilized to the same extent in adolescents despite the advantage of being non-invasive. Few novel studies have examined cutaneous thermal and mechanical sensations in healthy children (Blankenburg et al., 2010; Hilz et al., 1998; Meier, Berde, DiCanzio, Zurakowski, & Sethna, 2001). Further, peripheral neuropathic pain has been examined by QST in children with diabetes, idiopathic arthritis, sickle cell, familial dysautonomia, and complex regional pain syndrome (Blankenburg et al., 2010; Cornelissen et al., 2014; Jacob et al., 2015; Sethna, Meier, Zurakowski, & Berde, 2007).

Despite these studies establishing some QST reference values for children, major limitations include restricted sample sizes and the failure to separate results for age and gender. Huge gaps in the data exist due to the lack of reference values for a variety of sites on the body, with nearly all studies focusing on the face, hand, and/or foot. Chronic neuropathic pelvic pain secondary to endometriosis has not been explored via the use of QST and no reference values for QST pelvic pain thresholds exist. As an effort to fill the gaps in the database, this thesis explores the assessment of CPP via QST.

The Pain Sensitivity Questionnaire is another assessment tool for pain sensitivity (Ruscheweyh, Marziniak, Stumpfenhorst, Reinholz, & Knecht, 2009). The PSQ is a validated self-rating instrument for the assessment of pain sensitivity that is based on pain intensity ratings of imagined daily life situations (Ruscheweyh et al. 2009). Further, Ruscheweyh et al. went on to test the validity of the PSQ in patients specifically with chronic pain. Pain sensitivity was tested both via administration of QST and PSQ on chronic pain patients and healthy controls. Results showed a positive correlation between PSQ scores and experimental threshold pain scores from the QST (Ruscheweyh et al., 2012). Although PSQ measures and experimental pain testing are not identical measures, the PSQ offers another method of developing a measure of baseline pain sensitivity and pain perception in an easy 5-10 minute questionnaire that is non-invasive (Ruscheweyh et al., 2012). The combined use of both QST and the PSQ in understanding pain sensitivity when examining young women with CPP is a focus of this thesis.

Specific Aims and Objectives

This study aims to explore the relationships between psychophysical factors and postoperative chronic pelvic pain in young women with endometriosis. As a pilot study, there is large need to present preliminary data exploring the biopsychosocial correlates and possible predictors of central sensitization and CPP. These relationships have not been adequately investigated in adult humans and remain nonexistent in the realm of adolescents and young women with CPP secondary to endometriosis. Because this is a preliminary pilot study, the present investigation should be considered a hypothesis-generating study. However, based on previous literature in studies done on other body sites and in adult subjects, the following hypotheses may be suggested.

The specific aims of this study are:

AIM 1: To determine the subjects who have developed central sensitization, as detected by a wind-up phenomenon during the temporal summation of pain test, and explore any potential differences in psychophysical factors compared to the subjects who have not developed central sensitization.

Hypothesis 1: The group that is determined to have developed central sensitization will have higher mean pre-operative pain ratings, post-surgical pain, and sensitivity, and lower emotional and physical functioning.

AIM 2: To examine pre-surgical factors including pain ratings, emotional functioning, and physical functioning in relation to post-surgical pain and

sensitivity thresholds as measured by the PSQ (Ruscheweyh et al., 2009) and QST.

Hypothesis 2: Poor pre-surgical quality-of-life, emotional health and physical functioning as measured by the SF-36 (Ware, Kosinski, Dewey, & Gandek, 2000), and higher pre-surgical pain will correlate with higher post-surgical pain sensitivity and pain ratings in both cohorts, but more so in the group with suspected central sensitization.

AIM 3: Examine the effects of pre-surgical pain catastrophizing in relation to central sensitization and CPP secondary to endometriosis in a sub-sample of patients who have completed the PCS measure.

Hypothesis 3: High levels of catastrophizing will be correlated with higher post-surgical pain sensitivity and pain ratings in both cohorts, but more so in the group with suspected central sensitization.

METHODS

This study is a collaboration between the Biobehavioral Pediatric Pain Lab in the Pain Treatment Service at Boston Children's Hospital (BCH) and the Boston Center for Endometriosis (BCE). The Institutional Review Board approved this human study to administer and use data for clinical purposes within the program. The BCE began *The Women's Health Study: From Adolescence to Adulthood* in 2012 to explore health topics that affect women over their lifespan. The team has created a biorepository and a rich database including measurements of reproductive health, pain, and physical and emotional health. All patients above the age of 7 currently being treated for or who have undergone treatment for endometriosis at BCH or Brigham and Women's Hospital (BWH) are eligible to be approached about participating in the WHS, including patients with suspected endometriosis who are yet to undergo a diagnostic laparoscopy. Potentially eligible families were identified and approached at one of their clinical visits in the Department of Adolescent Medicine at BCH or BWH to obtain consent and assent to participate in the *WHS*.

This particular study focused on a subset of patients from the *Women's' Health Study* and obtained pre-surgical information from the WHS, added a postoperative sensory protocol to assess mechanical allodynia and pressure pain sensitivity, and collected a self-report measure of pain sensitivity.

Participants

Participants for this study were recruited from patients and parents, who are patients at BCH and currently enrolled in the BCE's *WHS: From Adolescence to Adulthood*. Inclusion criteria for this particular study included that patients were aged 12-22 years old and diagnosed with chronic pelvic pain after laparoscopic confirmation of endometriosis, presenting to the endometriosis clinic in the department of Adolescent Medicine. Potentially eligible families were identified and approached at one of their clinical visits at BCH by a research assistant working on the *WHS* to gauge interest. If interested, a research assistant from the Biobehavioral Pediatric Pain lab would then approach the patients and parents to obtain consent and assent to participate in this study. Another method of recruitment included sending research flyers to enrolled participants in the *WHS* who were eligible for this study as well. Patients who reached out to participate were scheduled for the study on a day that coincided with a follow-up appointment or any day that was most convenient for them.

Measures:

Baseline Survey

All participants completed baseline surveys as part of the *WHS*. These baseline surveys were intended to be pre-surgical, and were completed an average of 32.45 days (S.D. = 19.24) before laparoscopy for 20 of the 25 patients in the current study. The remaining 5 patients completed the survey an average of 63 days (S.D.= 51.09) after laparoscopy, but were instructed to answer questions based on how they were feeling

before the laparoscopy. Participants coming into BCH or BWH completed the self-administered questionnaire during the visit on a tablet or computer. Participants preferring to complete it at home completed the questionnaire online via a secure system or via a paper version and mailed it back to the study team. Questionnaires are then completed once per year indefinitely for the *WHS*, but only the initial baseline survey was used in the current study. Because the *WHS* has been ongoing for over 20 years, the questionnaire exists in different versions, and careful attention was taken to ensure consistent data points were taken among the different versions. The survey includes extensive questioning on demographics, menstruation and reproductive history, pain in various states, medical and family history, and lifestyle. Particular measures taken from the baseline survey for the present study include:

- ***36-Item Short Form Health Survey (SF-36)***: The SF-36 is a set of generic, coherent, and easily administered quality-of-life measures that can be scored to convey information about 8 health concepts: physical functioning (e.g. “How does your health limit you in moderate activities such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?”), bodily pain (e.g. “During the past 4 weeks, how much did pain interfere with your normal work?”), role limitations due to physical health problems (e.g. “During the past 4 weeks, have you accomplished less than you would like as a result of your physical health?”), role limitations due to personal or emotional problems (e.g. “During the past 4 weeks have you accomplished less than you would like as a result of emotional problems

such as feeling depressed or anxious?”), emotional well-being (e.g. “How much of the time during the past 4 weeks did you feel full of pep?”), social functioning (e.g. “During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities like visiting with friends, relatives, etc.?”), energy/fatigue (e.g. “How much of the time during the past 4 weeks did you feel tired?”), and general health perceptions (e.g. “How true or false is each of the following statements for you: I am as healthy as anyone I know. I expect my health to get worse, etc.”). It also includes a single item that provides an indication of perceived change in health. The SF-26 produces eight scaled scores, which are transformed into a 0-100 scale. Lower scores indicate increasing disability, while higher scores indicate less disability in a section (0 = maximum disability, 100 = no disability) (Ware et al., 2000). It has been validated, is used widely across medical disciplines, and can be self-administered by the patient with reliability (Patel, Donegan, & Albert, 2007).

- ***Pain Catastrophizing Scale (PCS)***: The Pain Catastrophizing Scale measures emotions individuals experience in response to their own pain and was used to assess the cognitions around pain. Analysis of this data can provide insight as to why some individuals, despite experiencing high pain and/or sensitivity, have better functioning than others. (Sullivan, Bishop, & Pivik, 1995). The PCS is measured on a five-point scale with

zero being “not at all” and four being “extremely.” The scores are summed, with greater scores indicating heightened catastrophic thinking in any three categories of rumination, magnification, and helplessness and an overall PCS-total score.

Pain Intensity

Participants were asked to rate their level of pain on a numerical eleven-point scale from 0 (no pain) to 10 (most pain possible). Due to differences in phrasing of this question, as pre-surgical documents have changed over time, different methods of obtaining an average “Pre-Surgical Pain Intensity” measure were necessary. Patients were either asked to report their pain score for the “Past 3 Months (average)” on the day of surgery or were asked their “Average Pain Score” during a pre-operative appointment which generally ranges from two weeks to two days before the procedure. Either available variable served as a measure of pre-surgical pain intensity for the purpose of this thesis.

Quantitative Sensory Testing (QST)

Patients underwent a brief sensory protocol devised by Navil Sethna, MD, who is an expert in QST in children and adolescents, in the department of Anesthesia and Pain Medicine at BCH (Cornelissen et al., 2014; Jacob et al., 2015; Meier et al., 2001; Sethna et al., 2007). With this protocol, pain sensitivity was measured by pain thresholds of the abdominal skin as assessed by the presence or absence of allodynia, a pain response to a

generally non-painful stimulus, and deeper abdominal muscular pain as assessed by a pressure pain threshold. The protocol was as follows:

- Participant was asked to delineate the pain over the abdomen and rate the pain on a numerical pain scale to the test stimuli
- Pain Threshold Tests. Each of the following tests was administered to the suspected painful area of the abdomen, which was broken down into four quadrants (lower left, lower right, upper left, upper right) (Figure 4). For the purpose of this thesis, the regions were analyzed as upper abdomen and lower abdomen.
 - Sensitivity was assessed by the use of Von Frey's hairs. The filaments were applied starting with the smallest weight (in grams) and diameter of von Frey's hairs, and gradually increased until the subject could successfully detect the filament touching their skin. The weight of the filament that was successfully detected served as a light touch detection threshold.
 - Muscular pain threshold was evaluated with the use of an electronic Algometer. The pressure pain threshold was performed using a method of limits that consisted of the gradual increase of pressure until the participant perceived the pressure as painful. The test was repeated 3 times and the pressure pain threshold was calculated as a mean of the three trials.

- The temporal summation test was performed to detect a wind-up phenomenon as a surrogate of central sensitization. Von Frey's hairs were applied to the painful area and the pressure is gradually increased using a method of limits until the participant perceives pain. This pain threshold stimulus is applied 10 times at 0.3Hz. Temporal summation is calculated as the ratio of the 10th stimulus to the 1st stimulus. Wind-up was determined if the ratio of the 10th:1st stimulus was increased.
 - These tests were also all applied to deltoid site as an internal control.
- Published QST data by Blankenburg et al., (2010) and Meier et al., (2001) involving healthy children and adolescents as control groups was also used to control for global change in pain sensitivity.

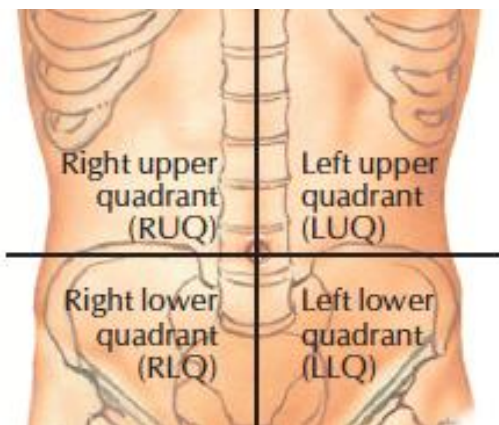


Figure 4. Four anatomical quadrants of the abdomen. Figure taken from (Netter, 2014).

Pain Sensitivity Questionnaire (PSQ)

The PSQ is a 17-item brief rating measure for pain perception based on imagined daily life situations, rated on a scale from 0, no pain, to 10, worst pain imaginable (Ruscheweyh et al., 2009). Each question requires the participants to put themselves in the situation of the question prior to answering. The scoring of the PSQ is divided into two scores which can be summed for a total score. PSQ-minor scores a subset of the questions that are constituted by items that are on average deemed as causing minor pain (scores <4 on the 11 point scale), while PSQ-major corresponds to the items on average rated as moderately painful (score 4-6) (Ruscheweyh et al., 2009). This is an easy way to measure pain sensitivity, as it does not require any equipment or administration from a staff member and is needed to subjectively measure pain sensitivity to be correlated with the more objective QST measure. Each participant filled out a paper copy of the PSQ prior to administration of QST.

RESULTS

Overall, there were 25 female participants ranging from 14-22 years old (mean age = 17.56, SD = 2.14), who began menarche between the ages of 10 and 15 (mean age=11.28, SD=1.21). All participants had surgically diagnosed endometriosis of stage I (88%) or II (12%) and subsequent CPP. Because a single staff physician, Dr. Laufer, cared for all patients, a uniform surgical-medical treatment approach was applied to all individuals. This is a pilot sample, and data collection is ongoing. Of the 24 available pain demographic data points (one baseline questionnaire was given in a short form and did not assess pain), descriptions of pain experiences of the patients are summarized in Table 2.

Table 2: Participant data on pain experiences.

		n	%
How much pain do you usually have with your periods/vaginal bleeding?	No Pain	0	0
	Mild Cramps	0	0
	Moderate Cramps	7	29.2
	Severe Cramps	17	70.8
When did you start having pain with periods?	With very first period	12	50.0
	Within 2 years of first period	11	45.8
	More than 2 years after first period	1	4.2
Have you seen a doctor for this pain?	Yes	23	95.8
	No	1	4.2
# of doctors seen for pain		Mean: 3.22 (SD: 1.278)	

Aim 1: To determine the subset of subjects who have developed central sensitization, as detected by a wind-up phenomenon during the temporal summation test, and explore any potential differences in psychophysical factors compared to the subjects who have not developed central sensitization.

The temporal summation test was performed to detect a wind-up phenomenon, which served as a surrogate of central sensitization. Temporal summation was calculated as the ratio of pain scores of the 10th stimulus to the 1st stimulus. An increased ratio, compared to the ratio at the deltoid control site of the subject, indicates the presence of a wind-up phenomenon in the abdomen, and thus central sensitization. 6 of the 25 patients (24%) experienced wind up phenomenon, with 5 of the 6 (83.33%) experiencing it in both the upper and lower abdominal regions, and 1 of the 6 experiencing it in only the lower region.

One-way analyses of variance (ANOVA) were performed to assess any potential differences in the mean values of psychophysical parameters tested between the two cohorts; subjects with suspected central sensitization (+CS) and subjects without central sensitization (-CS). Though apparent differences were present, all differences failed to reach significance at the 95% confidence interval. All parameter means are presented in Table 3.

Table 3: Psychophysical parameter means in population subsets

	No Central Sensitization		Central Sensitization	
PreOp Pain Intensity	4.90 ± 2.79		5.67 ± 1.51	
Quality of Life Measures				
SF36_Physical Functioning	76.84 ± 28.20		65.00 ± 30.82	
SF36_Role Limitations due to Physical Health	57.90 ± 47.91		35.00 ± 41.83	
SF36_Role Limitations due to Emotional Problems	63.16 ± 42.88		93.33 ± 14.91	
SF36_Energy & Fatigue	47.63 ± 21.63		35.00 ± 25.74	
SF36_Emotional Well-Being	64.42 ± 20.82		67.20 ± 31.16	
SF36_Social Functioning	61.18 ± 36.54		60.00 ± 36.87	
SF36_Bodily Pain	48.16 ± 29.13		56.00 ± 28.21	
SF36_General Health Perceptions	55.00 ± 24.94		50.00 ± 29.37	
QST Measures				
	Upper	Lower	Upper	Lower
Light Touch Threshold	1.36 ± 3.66	1.34 ± 3.72	0.29 ± 0.40	0.13 ± 0.16
Pinprick Threshold	24.76 ± 68.23	21.37 ± 68.23	38.48 ± 64.85	18.72 ± 39.91
Pinprick Pain Score	1.45 ± 1.33	1.39 ± 1.50	0.83 ± 0.75	0.83 ± 0.75
Pressure Pain Threshold	12.15 ± 4.87	13.28 ± 6.41	12.83 ± 6.66	13.08 ± 8.25
Pain Sensitivity Questionnaire Measures				
PSQ-total	3.97 ± 1.54		4.29 ± 1.18	
PSQ moderate	4.56 ± 1.75		4.94 ± 1.08	
PSQ minor	3.29 ± 1.69		3.29 ± 1.18	
Pain Catastrophizing Scale Measures				
PCS-total	43.93 ± 21.18		28.00 ± 16.39	
PCS-rumination	10.73 ± 5.22		6.00 ± 4.90	
PCS-magnification	4.47 ± 3.09		2.75 ± 1.71	
PCS-helplessness	28.73 ± 13.87		19.25 ± 10.40	

Aim 2: Examine pre-surgical factors including pain ratings, emotional functioning, and physical functioning in relation to post-surgical pain and sensitivity thresholds as measured by the PSQ and QST.

Bivariate Pearson correlations were used to assess relationships between pre-surgical psychosocial factors and post-surgical measures of pain intensity and sensitivity in the subject population as a whole, as well as each cohort (+CS and –CS). Pre-surgical factors included eight measures of health status from the SF-36 (physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions) and pre-surgical pain intensity. These measures were considered in relation to post-surgical pain sensitivity (measured by PSQ and QST: von Frey’s touch detection) and pain intensity (measured by QST: von Frey’s sharp prick threshold, sharp prick pain rating, and pressure pain threshold). In both cohorts, numerous correlations were noted among different measures of health status from the SF-36. QST variables also were correlated amongst one another in both cohorts. Pre-operative pain intensity was not correlated with any other variable in either cohort.

Among pre-operative and post-operative factors in the population as a whole, the SF-36 score for bodily pain was positively correlated with light touch detection thresholds of the upper and lower abdomen (Table 4). This remained true in the –CS cohort. In addition, the bodily pain SF-36 score was also positively correlated with pressure pain thresholds for both the upper and lower abdomen in the –CS cohort (Table 5). In the +CS group, SF-36 bodily pain score was positively correlated with light touch

detection of the lower region of the abdomen, and with pinprick pain scores of both the upper and lower regions of the abdomen. Further, role limitations due to physical health SF-36 score was positively correlated with light touch detection of the lower abdomen (Table 6).

Table 4. Correlations between pre-operative health factors and post-operative QST and PSQ in entire sample. Regions in white indicate correlations between pre-surgical and post-surgical variables.

Variable	2	3	4	5	6	7	8	9	10	11
1. PreOp Pain Intensity	-.177	-.127	-.140	-.127	.020	-.052	-.001	-.352	-.160	-.160
2. SF36_Physical Functioning		.686**	.518**	.611**	.561**	.689**	.348	.558**	.264	.279
3. SF36_Role Limitations due to Physical Health			.570**	.710**	.478*	.782**	.658**	.727**	.300	.314
4. SF36_Role Limitations due to Emotional Problems				.350	.524**	.604**	.397	.399	.200	.216
5. SF36_Energy & Fatigue					.781**	.693**	.380	.706**	.151	.173
6. SF36_Emoional Well-Being						.715**	.209	.568**	.203	.266
7. SF36_Social Functioning							.625**	.722**	.294	.322
8. SF36_Bodily Pain								.418*	.429*	.417*
9. SF36_General Health Perceptions									.331	.357
10. Light Touch Detection Upper Ab (VF)										.997**
11. Light Touch Detection Lower Ab (VF)										
12. Pinprick Threshold Upper Ab (VF)										
13. Pinprick Pain Score Upper Ab										
14. Pinprick Threshold Lower Ab (VF)										
15. Pinprick Pain Score Lower Ab										
16. Sensation of Pressure Pain Upper Ab										
17. Sensation of Pressure Pain Lower Ab										
18. PSQ_Minor										
19. PSQ_Moderate										
20. PSQ_Total										

Variable	12	13	14	15	16	17	18	19	20
1. PreOp Pain Intensity	.035	-.181	.010	-.193	.126	.265	-2.94	-.191	-2.63
2. SF36_Physical Functioning	.204	.180	.171	.081	.181	.171	-.133	-.163	-.133
3. SF36_Role Limitations due to Physical Health	.268	-.077	.240	-.169	.323	.302	-.244	-.231	-.215
4. SF36_Role Limitations due to Emotional Problems	.233	-.137	.171	-.200	.245	.193	-.205	-.119	-.142
5. SF36_Energy & Fatigue	.267	.314	.229	.272	.228	.253	-.099	-.196	-.135
6. SF36_Emoional Well-Being	.299	.118	.212	.077	.339	.282	.027	.023	.037
7. SF36_Social Functioning	.291	.007	.244	-.151	.380	.318	-.133	-.113	-.125
8. SF36_Bodily Pain	.324	-.027	.284	-.153	.356	.389	-.147	-.242	-.195
9. SF36_General Health Perceptions	.235	.166	.155	.066	.160	.057	.041	.092	.076
10. Light Touch Detection Upper Ab (VF)	.167	-.044	.045	-.022	.225	.085	.200	.198	.190
11. Light Touch Detection Lower Ab (VF)	.178	-.037	.056	-.021	.227	.083	.205	.211	.199
12. Pinprick Threshold Upper Ab (VF)		-.045	.962**	-.295	.333	.428*	-.092	-.019	-.071
13. Pinprick Pain Score Upper Ab			.016	.925**	-.536**	-.430*	.239	.183	.215
14. Pinprick Threshold Lower Ab (VF)				-.271	.223	.386	-.157	-.124	-.157
15. Pinprick Pain Score Lower Ab					.558**	.518**	.274	.204	.256
16. Sensation of Pressure Pain Upper Ab						.906**	-.117	-.059	-.094
17. Sensation of Pressure Pain Lower Ab							-.268	-.293	-.299
18. PSQ_Minor								.867**	.957**
19. PSQ_Moderate									.967**
20. PSQ_Total									

*p<0.05

**p<0.01

Table 5. Correlations between pre-operative health factors and post-operative QST and PSQ in –CS subset. Regions in white indicate correlations between pre-surgical and post-surgical variables.

Variable	2	3	4	5	6	7	8	9	10	11
1. PreOp Pain Intensity	-.156	-.035	-.205	-.101	-.007	-.001	.105	-.352	-.137	-.143
2. SF36_Physical Functioning		.677**	.649**	.532*	.485*	.670**	.406	.509*	.270	.285
3. SF36_Role Limitations due to Physical Health			.735**	.689**	.531*	.800**	.678**	.697**	.290	.310
4. SF36_Role Limitations due to Emotional Problems				.510*	.632**	.721**	.428	.511*	.254	.284
5. SF36_Energy & Fatigue					.797**	.668**	.466*	.633**	.141	.158
6. SF36_Emotional Well-Being						.694**	.315	.531*	.266	.287
7. SF36_Social Functioning							.686**	.754**	.323	.352
8. SF36_Bodily Pain								.414	.475*	.479*
9. SF36_General Health Perceptions									.363	.393
10. Light Touch Detection Upper Ab (VF)										.998**
11. Light Touch Detection Lower Ab (VF)										
12. Pinprick Threshold Upper Ab (VF)										
13. Pinprick Pain Score Upper Ab										
14. Pinprick Threshold Lower Ab (VF)										
15. Pinprick Pain Score Lower Ab										
16. Sensation of Pressure Pain Upper Ab										
17. Sensation of Pressure Pain Lower Ab										
18. PSQ_Minor										
19. PSQ_Moderate										
20. PSQ_Total										

Variable	12	13	14	15	16	17	18	19	20
1. PreOp Pain Intensity	-.010	-.106	.001	-.129	.020	.206	-.357	-.079	-.146
2. SF36_Physical Functioning	.202	.154	.172	.044	.090	.071	-.183	.001	-.022
3. SF36_Role Limitations due to Physical Health	.272	-.211	.239	-.298	.442	.413	-.218	-.075	-.110
4. SF36_Role Limitations due to Emotional Problems	.259	-.101	.225	-.179	.307	.241	-.186	-.022	-.102
5. SF36_Energy & Fatigue	.244	.294	.234	.254	.089	.124	-.032	-.138	-.107
6. SF36_Emotional Well-Being	.325	.177	.269	.119	.119	.041	.103	.124	.066
7. SF36_Social Functioning	.314	-.037	.273	-.212	.378	.306	-.074	.106	.016
8. SF36_Bodily Pain	.392	-.123	.336	-.258	.668**	.718**	-.056	-.056	-.062
9. SF36_General Health Perceptions	.219	.100	.164	-.007	.084	-.052	.167	.222	.164
10. Light Touch Detection Upper Ab (VF)	.214	-.095	.050	-.063	.320	.127	.201	.300	.295
11. Light Touch Detection Lower Ab (VF)	.216	-.082	.054	-.057	.299	.104	.207	.312	.302
12. Pinprick Threshold Upper Ab (VF)		.044	.983**	-.262	.260	.458*	.155	.312	-.181
13. Pinprick Pain Score Upper Ab			.063	.917**	-.562*	-.454	.381	.350	.323
14. Pinprick Threshold Lower Ab (VF)				-.258	.206	.452	.029	.164	-.253
15. Pinprick Pain Score Lower Ab					-.596**	-.568*	.332	.232	.320
16. Sensation of Pressure Pain Upper Ab						.877**	-.176	-.148	-.182
17. Sensation of Pressure Pain Lower Ab							-.301	-.362	-.375
18. PSQ_Minor								.838**	.950**
19. PSQ_Moderate									.954**
20. PSQ_Total									

*p<0.05

**p<0.01

Table 6. Correlations between pre-operative health factors and post-operative QST and PSQ in + CS subset. Regions in white indicate correlations between pre-surgical and post-surgical variables

Variable	2	3	4	5	6	7	8	9	10	11
1. PreOp Pain Intensity	-.218	-.732	.200	-.145	.127	-.435	-.943**	-.382	-.759	-.806
2. SF36_Physical Functioning		.679	.544	.819	.859	.811	.248	.711	.342	.618
3. SF36_Role Limitations due to Physical Health			.134	.755	.449	.780	.824	.890**	.643	.896*
4. SF36_Role Limitations due to Emotional Problems				.217	.273	-.038	-.030	.095	.432	.201
5. SF36_Energy & Fatigue					.879*	.873	.254	.951*	.086	.460
6. SF36_Emoional Well-Being						.825	-.121	.699	-.169	.230
7. SF36_Social Functioning							.379	.851	.146	.627
8. SF36_Bodily Pain								.509	.848	.896*
9. SF36_General Health Perceptions									.262	.609
10. Light Touch Detection Upper Ab (VF)										.688
11. Light Touch Detection Lower Ab (VF)										
12. Pinprick Threshold Upper Ab (VF)										
13. Pinprick Pain Score Upper Ab										
14. Pinprick Threshold Lower Ab (VF)										
15. Pinprick Pain Score Lower Ab										
16. Sensation of Pressure Pain Upper Ab										
17. Sensation of Pressure Pain Lower										
18. PSQ_Minor										
19. PSQ_Moderate										
20. PSQ_Total										

Variable	12	13	14	15	16	17	18	19	20
1. PreOp Pain Intensity	.266	-.765	.144	-.765	.646	.684	.192	.094	.082
2. SF36_Physical Functioning	.225	.229	-.069	.229	.442	.447	.255	.027	.326
3. SF36_Role Limitations due to Physical Health	.163	.845	-.062	.845	-.066	-.082	-.339	-.452	-.208
4. SF36_Role Limitations due to Emotional Problems	.287	.000	.388	.000	.161	.216	.523	n/a	.498
5. SF36_Energy & Fatigue	.596	.343	.234	.343	.604	.591	-.318	-.454	-.263
6. SF36_Emoional Well-Being	.452	-.091	.061	-.091	.809	.800	.056	-.030	.077
7. SF36_Social Functioning	.149	.360	-.267	.360	.403	.371	-.159	-.096	-.055
8. SF36_Bodily Pain	-.224	.971**	-.238	.971*	-.616	-.630	-.309	-.352	-.165
9. SF36_General Health Perceptions	.521	.602	.200	.602	.359	.339	-.495	-.590	-.411
10. Light Touch Detection Upper Ab (VF)	-.366	.793	-.300	.793	-.684	-.640	-.061	-.400	-.051
11. Light Touch Detection Lower Ab (VF)	.207	.495	.279	.495	-.225	-.317	.180	.178	.323
12. Pinprick Threshold Upper Ab (VF)		-.510	.959**	-.510	.546	.364	.416	.679	.565
13. Pinprick Pain Score Upper Ab			-.542	1.000**	-.600	-.518	-.641	-.701	-.598
14. Pinprick Threshold Lower Ab (VF)				-.542	.378	.171	.566	.836	.716
15. Pinprick Pain Score Lower Ab					-.600	-.518	-.641	-.701	-.598
16. Sensation of Pressure Pain Upper Ab						.974**	.182	.242	.195
17. Sensation of Pressure Pain Lower Ab							.081	.046	.052
18. PSQ_Minor								.912*	.972**
19. PSQ_Moderate									.975**
20. PSQ_Total									

*p<0.05

**p<0.001

One sample t-tests were conducted to compare mean values for QST testing between the internal control deltoid site and the painful areas of the abdomen. For the study population as a whole, the pressure pain threshold of the control (M= 25.211, SD=10.67) was significantly higher than the thresholds of the upper abdominal region (M=12.313, SD=5.21; t(24)= -12.386, p=0.00) and lower abdominal region (M=13.232, SD=6.71; t(24)= -8.926, p=0.00). Pressure pain thresholds of the upper and lower abdomen in the -CS and +CS cohorts were also significantly lower than the control deltoid site (-CS: upper; t(18)= -11.695, p=0.00. lower; t(18)= -8.111, p=0.00) (+CS: upper; t(5)= -4.552, p=0.006. lower; t(5)= -3.602, p=0.016)(Table 7).

When comparing PSQ data from the subject population to published means by Ruscheweyh et al. (2009), PSQ-minor scores for the entire population were significantly higher than published means; t(24) = 2.533, p=0.018. This difference failed to reach significance when analyzing each cohort separately, despite similar values in PSQ-minor scores (Table 7).

Table 7. QST and PSQ means

	Control Deltoid Mean	Overall		No Sensitization		Central Sensitization	
		Upper Mean	Lower Mean	Upper Mean	Lower Mean	Upper Mean	Lower Mean
Sensitivity							
Light Touch Threshold (g)	.208	1.101	1.049	1.356	1.341	.291	.124
Pain							
Sharp Prick Detection (g)	19.936	28.054	20.731	24.761	21.366	34.483	18.781
Sharp Prick Pain	1.040	1.300	1.260	1.447	1.395	0.833	0.833
Pressure Pain Threshold (N)	25.211	12.313**	13.232**	12.149**	13.281**	12.833**	13.017**
PSQ	Published Means	Subject Means					
PSQ-total	3.6 ± 1.2	4.0 ± 1.5		3.3±1.5		4.3 ± 1.2	
PSQ-moderate	4.7 ± 1.6	4.6 ± 1.5		4.6± 1.6		4.9 ± 1.2	
PSQ-minor	2.5 ± 1.1	3.3 ± 1.6*		3.3 ± 1.7		3.3 ± 1.2	

*p<0.05

**p<0.01

Aim 3: Examine the effects of pre-surgical pain catastrophizing in relation to central sensitization and CPP secondary to endometriosis in a sub-sample of patients who have completed the PCS measure.

Of the 25 patients enrolled, 19 had PCS measures completed as part of their baseline surveys. Table 6 exhibits the bivariate Pearson correlations for PCS scores and post-surgical measures of sensitivity and pain for the entire subject population (N=19). No significant correlations were found between any PCS scores and post-surgical measures. PCS sub-scores were shown to significantly correlate with one another (Table 8). These findings remained constant when analyzing the -CS cohort (N=15) (Table 9).

Analysis of the +CS cohort (N=4) revealed significant negative correlations between PCS-total score and pressure pain thresholds of both the upper and lower abdomen. PCS-rumination was also negatively correlated with the pressure pain threshold of the lower abdominal region in this group (Table 10).

Table 8. Correlations between PCS and post-operative QST and PSQ in entire sample. Regions in white indicate correlations between PCS (pre-surgical) and post-surgical variables.

Variable	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. PCS_Total	.934**	.834**	.993**	.019	-.012	-.110	.130	-.124	.141	-.261	-.078	-.058	-.160	-.155
2. PCS_Rumination		.679**	.901**	.180	.152	-.050	.107	-.079	.103	-.284	-.146	-.181	-.220	-.249
3. PCS_Magnification			.820**	-.186	-.211	-.248	.095	-.243	.067	-.108	.109	.174	-.058	.022
4. PCS_Helplessness				-.002	-.033	-.097	.138	-.109	.162	-.267	-.085	-.054	-.147	-.146
5. Light Touch Detection Upper Ab (VF)					.997**	.167	.044	.045	-.022	.225	.085	.200	.198	.190
6. Light Touch Detection Lower Ab (VF)						.178	.037	.056	-.021	.227	.083	.205	.211	.199
7. Pinprick Threshold Upper Ab (VF)							.045	.962**	-.295	.333	.428*	-.092	-.019	-.071
8. Pinprick Pain Score Upper									.925**	.536**	-.430*	.239	.183	.215
9. Pinprick Threshold Lower Ab (VF)									-.217	.233	.386	-.157	-.124	-.157
10. Pinprick Pain Score Lower										.558**	.518**	.274	.204	.256
11. Sensation of Pressure Pain Upper Ab											.906**	-.117	-.059	-.094
12. Sensation of Pressure Pain Lower												-.268	-.293	-.299
13. PSQ_Minor													.867**	.957**
14. PSQ_Moderate														.967**
15. PSQ_Total														

*p<0.05

**p<0.01

Table 9. Correlations between PCS and post-operative QST and PSQ in -CS subset. Regions in white indicate correlations between PCS (pre-surgical) and post-surgical variables.

Variable	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. PCS_Total	.929**	.831**	.993**	-.045	-.076	.166	.014	.197	.034	-.167	.039	.100	.001	.011
2. PCS_Rumination		.651**	.897**	.129	.102	.316	-.061	.344	-.054	-.187	-.031	-.017	-.052	-.084
3. PCS_Magnification			.801**	-.248	-.273	-.088	.015	-.066	-.012	-.014	.217	.316	.090	.182
4. PCS_Helplessness				-.062	-.094	.155	.040	.186	.075	-.182	.023	.089	.000	.008
5. Light Touch Detection Upper Ab (VF)					.998*	.214	-.095	.050	-.063	.320	.127	.201	.300	.295
6. Light Touch Detection Lower Ab (VF)						.216	-.082	.054	-.057	.299	.104	.207	.312	.302
7. Pinprick Threshold Upper Ab (VF)							.044	.983**	-.262	.260	.458*	.155	.312	-.181
8. Pinprick Pain Score Upper								.063	.917**	-.562*	-.454	.381	.350	.323
9. Pinprick Threshold Lower Ab (VF)									-.258	.206	.452	.029	.164	-.253
10. Pinprick Pain Score Lower										.596**	-.568*	.332	.232	.320
11. Sensation of Pressure Pain Upper Ab											.877**	-.176	-.148	-.182
12. Sensation of Pressure Pain Lower												-.301	-.362	-.375
13. PSQ_Minor													.838**	.950**
14. PSQ_Moderate														.954**
15. PSQ_Total														

*p<0.05

**p<0.01

Table 10. Correlations between PCS and post-operative QST and PSQ in +CS subset. Regions in white indicate correlations between PCS (pre-surgical) and post-surgical variables.

Variable	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. PCS_Total	.930	.893	.991**	.693	.073	-.345	.680	-3.41	.680	-.959*	-.981*	-.873	-.584	-.782
2. PCS_Rumination		.717	.876	.862	.435	-.258	.853	-.256	.853	-.922	-.982*	-.915	-.639	-.718
3. PCS_Magnification			.905	.571	-.257	-.663	.561	.660	.561	-.920	-.832	-.824	-.848	-.910
4. PCS_Helplessness				.592	-.047	-.313	.577	-.309	.577	-.925	-.947	-.809	-.638	-.745
5. Light Touch Detection Upper Ab (VF)					.688	-.366	.793	-.300	.793	-.684	-.640	-.061	-.400	-.051
6. Light Touch Detection Lower Ab (VF)						.207	.495	.279	.495	-.225	-.317	.180	.178	.323
7. Pinprick Threshold Upper Ab (VF)							-.510	.959**	-.510	.546	.364	.416	.679	.565
8. Pinprick Pain Score Upper								-.542	1.000**	-.600	-.518	-.641	-.701	-.598
9. Pinprick Threshold Lower Ab (VF)									-.542	.378	.171	.566	.836	.716
10. Pinprick Pain Score Lower										-.600	-.518	-.641	-.701	-.598
11. Sensation of Pressure Pain Upper Ab											.974**	.182	.242	.195
12. Sensation of Pressure Pain Lower												.081	.046	.052
13. PSQ_Minor													.912*	.972**
14. PSQ_Moderate														.975**
15. PSQ_Total														

*p<0.05

**p<0.01

The PCS User Manual only defines a mean score in a healthy population for the PCS-total score (M=20.9, SD=12.5) (Sullivan, 2009). One sample t-test analysis revealed that the overall study population had a significantly higher mean PCS-total score (M=40.57, SD=20.93; $t(18) = 4.097$, $p=.001$). Independently, the –CS group also had a significantly higher mean PCS-total score (M=49.93, SD=21.18; $t(14)=4.211$; $p=.001$). The +CS group did not present with a significant difference. The PCS User Manual (Sullivan, 2009) also defines “cut-off scores” for clinically relevant levels of catastrophizing. Table 10 illustrates the frequency of study participants who scored above the threshold of clinically relevant levels of catastrophizing (Sullivan, 2009).

Table 11. Frequency of participants with clinically relevant catastrophizing

Clinical Significance Value	% of Subjects with Clinically Significant Scores (N=19)
PCS-total ≥ 30	68.4
PCS-Rumination ≥ 11	42.1
PCS-Magnification ≥ 5	36.8
PCS-Helplessness ≥ 8	94.7

DISCUSSION

Despite common misconceptions, endometriosis is a prevalent disease known to affect adolescent and young women in addition to adult women. Due to atypical presentation of the disease in adolescents; delayed diagnosis, high rates of misdiagnosis, and delayed treatment are common public health concerns in this patient population (Youngster et al., 2013). Though many patients respond well to surgical intervention followed by hormonal therapy, a subset of patients develop chronic pelvic pain that becomes unresponsive to standard medical and surgical therapies, believed to be due to central sensitization (Doyle et al., 2009; Giamberardino et al., 2014). These patients continue to experience significant pain and disability, such as missed school and activities, decreased feelings of accomplishment, and decreased general well-being, often leading to symptoms of depression and anxiety.

This study aimed to contribute preliminary data towards elucidating the psychophysical factors that contribute to CPP and central sensitization in a sample of post-surgical young women with endometriosis and CPP. Systematic evaluation of pain sensitivity of painful abdominal and non-painful control sites and how they interact with psychosocial functioning could be important for monitoring clinical progress of CPP and response to treatment. Not only has this association not been adequately investigated in adult humans, but also no studies exist looking at adolescents and young adults with CPP secondary to endometriosis

Participants in this study sought out an average of 3.22 doctors for pain, despite all of them describing their pain as moderate (29.2%) or severe (70.8%). Nearly all subjects (98.3%) began experiencing pain within the first two years of menarche. According to previous literature, patients experiencing pain symptoms that start one year or later after menarche and persist despite treatment with NSAIDs and/or oral contraceptive pills are at an increased risk for having underlying endometriosis (Laufer et al., 2003; Saridoğan, 2015). The ability to more efficiently and effectively identify adolescents who are at heightened risk for endometriosis, and thus heightened risk for developing secondary CPP, could allow for sooner intervention and the ability to personalize treatment to help avoid the debilitating development of chronic pain.

The objective of this study specifically was to explore how pre-surgical physical and psychosocial health factors are related to pain sensitivity and intensity in young women with chronic pelvic pain secondary to endometriosis. Further, as a pilot study, preliminary data from quantitative sensory testing of the abdomen was presented as the first of its kind. Any significant differences between a mean internal control site compared to subjects' abdominal values were also considered. This subject population also presented with two subsets: those who tested positive for a wind-up phenomenon, implying central sensitization, and those who did not. All similarities and differences between the two subsets were also considered.

Although this was the first study of its kind, results from similar studies exploring psychophysical factors in children and adults of differing pain states were used to hypothesize that poor pre-surgical quality-of-life factors, as measured by the SF-36

(Ware, Kosinski, Dewey, & Gandek, 2000), high pre-surgical pain, and high levels of catastrophizing, as measured by the PCS (Sullivan et al., 1995), would correlate with higher pain sensitivity and pain ratings post-surgery as measured by QST and the PSQ (Ruscheweyh et al., 2012).

During the temporal summation of pain test, 6 of 25 (24%) subjects presented with wind-up phenomenon, which serves as a surrogate for central sensitization. Wind-up refers to the progressive increase in the magnitude of C-fiber evoked responses of dorsal horn neurons due to repetitive activation. The resulting response is a progressive increase in the magnitude of the sensory response (Li, Simone, & Larson, 1999). Though wind-up and central sensitization are not identical, based on similarities in transmitters and underlying pathways, wind-up during temporal summation has been proposed to be an initiator and index of central sensitization (Li et al., 1999). Subjects were deemed to have wind-up if the ratio of the pain scores for the 10th prick (after temporal summation) to the 1st prick was increased in comparison to the deltoid control site.

When comparing psychophysical factors between the +CS and –CS groups, differences seemed apparent, but no differences reached significance at the 95% confidence interval, likely due to the small sample sizes (N=6 and N=19). Though not reaching significance, the +CS group had notably lower light touch detection thresholds of both the upper and lower abdomen compared to the –CS group. This indicates that the perceived magnitude of the sensory response to the stimulus was greater for the +CS group than the –CS group, as to be expected to due to the sustained central neural network hypersensitivity caused by central sensitization (Simis et al., 2015).

Due to the low number of participants enrolled, this study did not yield many significant correlations between pre-surgical and post-surgical factors. Most measures presented internal correlations, such as between the eight subsets of the SF-36 with one another and the sub scores of the PSQ, indicative of internal consistency. Similarly, individual QST test points had many correlations with one another. Between pre-surgical health factors and post-surgical variables, a few significant correlations emerged.

In the patient population as a whole, the only significant correlation was between the SF-36 bodily pain score and the light touch detection thresholds of the upper and lower abdomen. In the patient population that did not present with apparent central sensitization, bodily pain SF-36 score was positively correlated with light touch detection thresholds and pressure pain thresholds for both the upper and lower abdomen. Higher scores on the SF-36 indicate a more positive health status and lower levels of disability. When defining the correlations, this means that the lower levels of bodily pain and decreased limitations due to bodily pain were correlated with increased muscular pain thresholds and decreased touch sensitivity of the abdomen. Correspondingly, increased levels of bodily pain and increased disability due to bodily pain was correlated with decreased muscular pain thresholds and increased touch sensitivity of the abdomen. If the bodily pain subset of the SF-36 is considered as a measure of pre-operative pain, this is in agreement with the literature that high preoperative pain sensitivity has been found to parallel increased risk for the development of chronic pain because these pain thresholds can be further reduced (Nielsen et al., 2008).

In the group expressing central sensitization, the bodily pain SF-36 score, similar to the –CS cohort, was positively correlated with the light touch detection threshold of lower abdomen, suggesting that increased disability due to bodily pain was linked to increased sensitivity. The SF-36 score for role limitations due to physical health problems was also correlated with light touch detection thresholds of the lower abdomen, indicating that decreased levels of disability due to role limitations by physical health are associated with decreased sensitivity of the lower abdomen. Increases in role limitations due to physical health can lead to significant disability, including missed school, associated depression, anxiety, and further perpetuation and intensify the overall pain experience (Greco, 2003; Smorgick et al., 2013). According to the literature, high levels of bodily pain would be expected to evoke changes in the spinal segments that innervate the pelvic region, causing a heightened sensitivity of peripheral pain receptors at the level of the skin (Jarrell & Arendt-Nielsen, 2013; Simis et al., 2015; Whitaker et al., 2016). The physiological stress of these psychosocial responses can further exacerbate the reactivity of the nervous system, leading to a heightened predisposition to the development of central sensitization (Diatchenko, Nackley, Slade, Fillingim, & Maixner, 2006).

Interestingly, increased SF-36 bodily pain scores (decreased levels and limitations) were correlated with increasing pinprick pain scores in the +CS cohort. This is contradictory to other correlations seen in this cohort. It would be expected that since the light touch detection threshold decreased with increasing bodily pain disability, the increased sensitivity of the skin would result in higher levels of pinprick pain. Further,

the preoperative numerical pain intensity rating was not significantly correlated with any other variable in either cohort. It would be expected that heightened pre-surgical pain would create conditions that are more susceptible to the development of CPP via central sensitization and result in heightened levels of neuropathic pain (Simis et al., 2015). Although the correlation did not reach significance, this relationship is seen in the +CS group with increasing pre-operative pain ratings trending with decreasing light touch detection thresholds (increasing sensitivity) of the upper and lower abdomen ($r=-.759$, $r=-.806$ respectively), compared to the -CS group having much weaker correlations ($r=-.127$, $r=-.143$). The overall lack of significant correlations goes against current data demonstrating a significant positive correlation between preoperative and post-operative pain intensity (Ip, Abrishami, Peng, Wong, & Chung, 2009), particularly in a population with visceral disease such as endometriosis, which can lead to increased continuous pain and larger areas of referred pain (Nielsen et al., 2008; Jarrel & Arendt-Nielsen, 2013). However, most previous studies have used psychophysical pain assessment for the determination of pre-operative pain, instead of a numerical pain scale rating, suggesting better options for pre-operative pain assessment (Ip et al., 2009; Nielsen et al., 2008). This, coupled with small sample sizes, might attribute to the lack of conclusive data supporting the previous literature on this relationship. Theoretically, preoperative pain caused by the initial endometriosis would have resulted in the increased release of various cytokines, that are known activators nociceptors, causing increased pain sensitivity and an upregulation of inflammatory cytokines, lending to a vicious cycle (Jarrell & Arendt-Nielsen, 2013; Moshiree, Zhou, Price, & Verne, 2006; Vergnolle,

2008; Edwards et al., 2008). Analysis of cytokine levels would help gain a better understanding of the process by which pre-operative pain is related to central sensitization and CPP in this population, and is a future direction of the work done in this thesis.

Analysis of QST data between the deltoid control site and painful abdominal regions also showed some significant differences in both cohorts. Because no QST data exists for the abdominal region in children or adults, the controls were taken to be the average of the deltoid measurements among the overall subject population for each test. Pressure pain sensitivity was significantly greater in the abdomen than at the deltoid control site in the +CS cohort, -CS cohort, and overall population, indicating a lower muscular pain threshold in the painful region of the abdomen. This is particularly interesting because a study done by As-Sanie et al. (2013) showed that peripheral pressure pain thresholds were also lower in women with CPP when compared to both women with endometriosis and no CPP and pain-free women. This proposes that the control deltoid site pressure threshold might be even lower in this population than a healthy control population, suggesting an even greater difference between the abdomen and periphery. Development of healthy control QST data at abdominal sites would allow for better analysis and stronger interpretations of these findings.

PSQ data also revealed significantly higher PSQ-minor scores among all population divisions when compared to published means. The PSQ-minor scores a subset of questions that are constituted by items that are on average deemed as causing minor pain (scores <4 on the 11 point scale). This indicates that on average, subjects in this

study considered hypothetically mildly painful stimuli to be more painful than the general population. The PSQ-minor score has high correlations with pain intensity ratings of experimental stimuli in healthy subjects and patients with chronic pain (Ruscheweyh et al., 2012). However, previous literature indicates that females score significantly higher than males on the PSQ-minor, but not on the PSQ-total or PSQ-moderate (Ruscheweyh et al., 2012), suggesting the need for more a specific control value for this study since all participants were young women.

Pain catastrophizing also revealed interesting findings, particularly in the +CS group. When analyzed as an entire subject population, no significant correlations were noted between the PCS and any post-operative QST measures or PSQ. The PCS sub-scores all correlated with one another, which was to be expected based on prior research on the reliability and internal consistency of the measure (Sullivan et al., 1995). This remained true in the –CS group as well. When the +CS group was analyzed as a separate entity, the PCS-total scores were negatively correlated with pressure pain thresholds of the upper and lower abdomen and PCS-rumination (“I can’t stop thinking about how much it hurts” (Sullivan, 2009)) scores were negatively correlated with pressure pain thresholds of the lower abdomen. Even though these correlations should be interpreted with caution due to an extremely small sample size (N=4), the effects of catastrophizing are of particular interest when considering central sensitization. Furthermore, the overall subject population had a significantly greater PCS-total score than the published mean for a healthy population (Sullivan et al., 1995). Also, a staggering percentage of participants

had clinically significant levels of catastrophizing with 68.4% having a PCS-total score and 94.7% having a PCS-helplessness score above the ‘cut-off.’

Catastrophizing has emerged as an important determining factor in pain-related outcomes and is consistently associated with higher pain levels due to its support in the development of central sensitization (Carey et al., 2014; Martin et al., 2011). Particularly, a high level of catastrophizing is hypothesized to disrupt endogenous pain-inhibitory pathways (Sullivan et al., 2001), increase neural activity in pain-processing regions of the brain (Martin et al., 2011), and is correlated with increased levels of inflammatory cytokines (Edwards et al., 2008; Yin et al., 2005). This suggests that future studies with larger sample sizes are warranted to further understand these relationships. Particular to endometriosis as an inflammatory process, the further study of high levels of catastrophization in relation to increased responsiveness to painful stimuli due to increased levels of cytokines is important for elucidating long-term pain outcomes.

Future Directions

As the first of its kind, there are many future directions for this study. One particular direction would be to establish QST norms from a healthy control population for various body sites, including the abdomen. Although control reference values do exist from healthy children, they were only gathered for the hand, face, and foot. Furthermore, significant differences between the aforementioned body sites indicated the need for separate sets of QST data when comparing different body sites (Blankenburg et al., 2010). Furthermore, a study done in adult women with endometriosis showed that not

only did pressure pain thresholds decrease in the painful abdomen site, but also at an internal control site on the finger (As-Sanie et al., 2013). This indicates that in order to appropriately examine QST values from adolescents with CPP, we first need to effectively develop control values from healthy individuals. Another future direction imperative to the assessment of this patient population would be the validation of the use of the PSQ within a child population. Although the PSQ proves to be valid for discerning pain sensitivity in adults (Ruscheweyh et al., 2012), differences in pain sensitivity have been shown to occur between genders and across age groups (Crombez et al., 2003).

Other future directions point toward the biology of pain. Particularly with central sensitization believed to play a significant role in the development of CPP (Giamberardino et al., 2014; Simis et al., 2015; Whitaker et al., 2016), exploring the biological substrates of sensitization is imperative. Measurements of cytokines levels in blood samples from patients should be carried out to assess their possible impact on nociceptors and their ability to cause increased pain (Jarrell & Arendt-Nielsen, 2013; Moshiree et al., 2006; Vergnolle, 2008). This is of particular interest for analyzing endometriosis as a visceral and inflammatory process. Visceral pain, catastrophizing, and inflammation have all been linked to the upregulation of cytokines that are known to activate nociceptive receptors and potentiate pain (Edwards et al., 2008; Ip et al., 2009; Jarrell & Arendt-Nielsen, 2013). As part of the *Women's Health Study*, a blood sample is taken from each subject and will eventually be analyzed for cytokines as this current study expands.

Limitations

As a pilot study with ongoing data collection, this present study used a small sample and thus was underpowered. Although recruitment strategies have been successful, our ability to recruit a large number of patients in a small window of time was diminished because recruitment started in late September and was dependent on patient visits to the clinic, which occurred only two days a week. As the *Women's Health Study* is a long-standing study, various versions of the questionnaire exist. Differences in which questions were asked and how they were phrased limited the number of consistent variables that were available for use in analyses. Furthermore, because this is an ongoing study, not all patients have extensive follow-up data as of yet to consider a more longitudinal approach. In summary, a larger sample size is needed to further explore how all the variables studied in our project are related.

Other limitations include the lack of validated measures for pediatric PSQ data and controls for abdominal QST in abdominal regions in pediatric population. This could contribute to the lack of correlations among these variables despite such findings in adult populations with different forms of chronic pain. Furthermore, QST was performed by four research assistants, suggesting a possible bias from each person, which could have resulted in inconsistencies and possible errors in the administration of the test. This has been a concern when assessing the reliability of QST in previous studies (Moloney, Hall, & Doody, 2012). With the current QST protocol, patients generally responded with minimal, if not 0, pain scores in response to sharp prick thresholds. This was limiting when considering increases or differences in pain intensity. Addition of another pain

rating with QST, such as the addition of a numeric pain scale rating following the pressure pain threshold or a test for heat and cold pain, could possibly lead to larger variance among pain ratings. Another way to assess levels of chronic pelvic pain is to add a post-operative numerical pain scale question to compare to the same question asked pre-surgery. This has been added to the protocol at the time of this thesis' submission.

Despite these limitations, the preliminary data presented in this thesis suggest the importance of pre-surgical pain and psychosocial functioning on post-surgical outcomes, particularly when considering subjects presenting with central sensitization. The QST abdominal assessment was the first of it's kind. Although few correlations and differences were found, the significance of the findings provide insight into possible future directions to consider in the assessment of chronic pelvic pain secondary to endometriosis in an adolescent population.

REFERENCES

- Abbott, J., Hawe, J., Hunter, D., Holmes, M., Finn, P., & Garry, R. (2004). Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. *Fertility and Sterility*, 82(4), 878–884.
- American College of Obstetricians and Gynecologists. (2005). ACOG Committee Opinion. Number 310, April 2005. Endometriosis in adolescents. *Obstetrics and Gynecology*, 105(4), 921–927.
- Aredo, J. V., Heyrana, K. J., Karp, B. I., Shah, J. P., & Stratton, P. (2017). Relating Chronic Pelvic Pain and Endometriosis to Signs of Sensitization and Myofascial Pain and Dysfunction. *Seminars in Reproductive Medicine*, 35(01), 088–097.
- As-Sanie, S., Harris, R. E., Harte, S. E., Tu, F. F., Neshewat, G., & Clauw, D. J. (2013). Increased pressure pain sensitivity in women with chronic pelvic pain. *Obstetrics and Gynecology*, 122(5), 1047–1055.
- Backonja, M. M., Attal, N., Baron, R., Bouhassira, D., Drangholt, M., Dyck, P. J., ... Ziegler, D. (2013). Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. *Pain*, 154(9), 1807–1819.
- Ballweg, M. L. (2003). Big picture of endometriosis helps provide guidance on approach to teens: comparative historical data show endo starting younger, is more severe. *ResearchGate*, 16(3 Suppl), S21–S26.
- Batt, R. E., & Mitwally, M. F. M. (2003). Endometriosis from thelarche to midteens: pathogenesis and prognosis, prevention and pedagogy. *Journal of Pediatric and Adolescent Gynecology*, 16(6), 337–347.
- Berkley, K. J., Cason, A., Jacobs, H., Bradshaw, H., & Wood, E. (2001). Vaginal hyperalgesia in a rat model of endometriosis. *Neuroscience Letters*, 306(3), 185–188.
- Berkley, K. J., Robbins, A., & Sato, Y. (1993). Functional differences between afferent fibers in the hypogastric and pelvic nerves innervating female reproductive organs in the rat. *Journal of Neurophysiology*, 69(2), 533–544.
- Blankenburg, M., Boekens, H., Hechler, T., Maier, C., Krumova, E., Scherens, A., ... Zernikow, B. (2010). [Reference values for quantitative sensory testing in children and adolescents : Developmental and gender differences in somatosensory perception]. *Schmerz (Berlin, Germany)*, 24(4), 380–382.

- Boey, C. C., & Goh, K. L. (2001). Predictors of recurrent abdominal pain among 9 to 15-year-old urban school-children in Malaysia. *Acta Paediatrica (Oslo, Norway: 1992)*, *90*(3), 353–355.
- Carey, E. T., Martin, C. E., Siedhoff, M. T., Bair, E. D., & As-Sanie, S. (2014). Biopsychosocial correlates of persistent postsurgical pain in women with endometriosis. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics*, *124*(2), 169–173.
- Celedon, X., Amari, A., Ward, C. M., Prestwich, S., & Slifer, K. J. (2014). Children and Adolescents with Chronic Pain and Functional Disability: Use of a Behavioral Rehabilitation Approach. *Current Physical Medicine and Rehabilitation Reports*, *2*(2), 86–92.
- Coccia, M. E., Rizzello, F., Palagianò, A., & Scarselli, G. (2011). Long-term follow-up after laparoscopic treatment for endometriosis: multivariate analysis of predictive factors for recurrence of endometriotic lesions and pain. *European Journal of Obstetrics and Gynecology and Reproductive Biology*, *157*(1), 78–83.
- 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*, 39.
- Crombez, G., Bijttebier, P., Eccleston, C., Mascagni, T., Mertens, G., Goubert, L., & Verstraeten, K. (2003). The child version of the pain catastrophizing scale (PCS-C): a preliminary validation. *Pain*, *104*(3), 639–646.
- Diatchenko, L., Nackley, A. G., Slade, G. D., Fillingim, R. B., & Maixner, W. (2006). Idiopathic pain disorders--pathways of vulnerability. *Pain*, *123*(3), 226–230.
- 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.
- Edwards, R. R., Kronfli, T., Haythornthwaite, J. A., Smith, M. T., McGuire, L., & Page, G. G. (2008). Association of catastrophizing with interleukin-6 responses to acute pain. *Pain*, *140*(1), 135–144.
- Evans, S., Tsao, J. C. I., Lu, Q., Myers, C., Suresh, J., & Zeltzer, L. K. (2008). Parent-Child Pain Relationships from a Psychosocial Perspective: A Review of the Literature. *Journal of Pain Management*, *1*(3), 237–246.

- Gambone, J. C., Mittman, B. S., Munro, M. G., Scialli, A. R., & Winkel, C. A. (2002). Consensus statement for the management of chronic pelvic pain and endometriosis: proceedings of an expert-panel consensus process. *Fertility and Sterility*, 78(5), 961–972.
- Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: Scientific advances and future directions. *Psychological Bulletin*, 133(4), 581–624.
- Giamberardino, M. A., Tana, C., & Costantini, R. (2014). Pain thresholds in women with chronic pelvic pain. *Current Opinion in Obstetrics & Gynecology*, 26(4), 253–259.
- Goldstein, D. P., deCholnoky, C., Leventhal, J. M., & Emans, S. J. (1979). New insights into the old problem of chronic pelvic pain. *Journal of Pediatric Surgery*, 14(6), 675–680.
- Greco, C. D. (2003). Management of adolescent chronic pelvic pain from endometriosis: a pain center perspective. *Journal of Pediatric and Adolescent Gynecology*, 16(3 Suppl), S17-19.
- Hilz, M. J., Stemper, B., Schweibold, G., Neuner, I., Grahmann, F., & Kolodny, E. H. (1998). Quantitative thermal perception testing in 225 children and juveniles. *Journal of Clinical Neurophysiology: Official Publication of the American Electroencephalographic Society*, 15(6), 529–534.
- Hurd, W. W. (1998). Criteria that indicate endometriosis is the cause of chronic pelvic pain. *Obstetrics & Gynecology*, 92(6), 1029–1032.
- Ip, H. Y. V., Abrishami, A., Peng, P. W. H., Wong, J., & Chung, F. (2009). Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology*, 111(3), 657–677.
- Jacob, E., Chan, V. W., Hodge, C., Zeltzer, L., Zurakowski, D., & Sethna, N. F. (2015). Sensory and Thermal Quantitative Testing in Children With Sickle Cell Disease. *Journal of Pediatric Hematology/Oncology*, 37(3), 185–189.
- Jarrell, J., & Arendt-Nielsen, L. (2013). Quantitative sensory testing in gynaecology: improving preoperative and postoperative pain diagnosis. *Journal of Obstetrics and Gynaecology Canada: JOGC = Journal D'obstetrique et Gynecologie Du Canada: JOGC*, 35(6), 531–535.

- Kontoravdis, A., Hassan, E., Hassiakos, D., Botsis, D., Kontoravdis, N., & Creatsas, G. (1999). Laparoscopic evaluation and management of chronic pelvic pain during adolescence. *ResearchGate*, 26(2), 76–7.
- Laufer. (2000). Premenarcheal Endometriosis Without an Associated Obstructive Anomaly: Presentation, Diagnosis, and Treatment. *Fertility and Sterility*, 74(3), S15.
- Laufer, 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, Sanfilippo, J., & Rose, G. (2003). Adolescent endometriosis: diagnosis and treatment approaches. *Journal of Pediatric and Adolescent Gynecology*, 16(3 Suppl), S3-11.
- Li, J., Simone, D. A., & Larson, A. A. (1999). Windup leads to characteristics of central sensitization. *Pain*, 79(1), 75–82.
- Martin, C. E., Johnson, E., Wechter, M. E., Leserman, J., & Zolnoun, D. A. (2011). Catastrophizing: a predictor of persistent pain among women with endometriosis at 1 year. *Human Reproduction*, 26(11), 3078–3084.
- Mavrelou, D., & Saridogan, E. (2013). Current therapeutic approaches to managing dysmenorrhoea. *ResearchGate*, 24(12).
- McAllister, Murray J. "Central Sensitization." *Understanding Chronic Pain*. Institute for Chronic Pain, 27 Apr. 2012.
- McLean, S. A., Clauw, D. J., Abelson, J. L., & Liberzon, I. (2005). The development of persistent pain and psychological morbidity after motor vehicle collision: integrating the potential role of stress response systems into a biopsychosocial model. *Psychosomatic Medicine*, 67(5), 783–790.
- Meier, P. M., Berde, C. B., DiCanzio, J., Zurakowski, D., & Sethna, N. F. (2001). Quantitative assessment of cutaneous thermal and vibration sensation and thermal pain detection thresholds in healthy children and adolescents. *Muscle & Nerve*, 24(10), 1339–1345.
- Moloney, N. A., Hall, T. M., & Doody, C. M. (2012). Reliability of thermal quantitative sensory testing: a systematic review. *Journal of Rehabilitation Research and Development*, 49(2), 191–207.

- Moshiree, B., Zhou, Q., Price, D. D., & Verne, G. N. (2006). Central sensitisation in visceral pain disorders. *Gut*, *55*(7), 905–908.
- Netter, Frank H. *Atlas of Human Anatomy*. Philadelphia, PA: Saunders/Elsevier, 2014.
- Nielsen, C. S., Stubhaug, A., Price, D. D., Vassend, O., Czajkowski, N., & Harris, J. R. (2008). Individual differences in pain sensitivity: genetic and environmental contributions. *Pain*, *136*(1–2), 21–29.
- Patel, A. A., Donegan, D., & Albert, T. (2007). The 36-item short form. *The Journal of the American Academy of Orthopaedic Surgeons*, *15*(2), 126–134.
- Phillips, K., & Clauw, D. J. (2011). Central pain mechanisms in chronic pain states – Maybe it is all in their head. *Best Practice & Research Clinical Rheumatology*, *25*(2), 141–154.
- Poleshuck, E. L., Talbot, N. E., Zlotnick, C., Gamble, S. A., Liu, X., Tu, X., & Giles, D. E. (2010). Interpersonal psychotherapy for women with comorbid depression and chronic pain. *The Journal of Nervous and Mental Disease*, *198*(8), 597–600.
- Powell, J. (2014). The approach to chronic pelvic pain in the adolescent. *Obstetrics and Gynecology Clinics of North America*, *41*(3), 343–355.
- 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.
- Ruscheweyh, R., Marziniak, M., Stumpfenhorst, F., Reinholz, J., & Knecht, S. (2009). Pain sensitivity can be assessed by self-rating: Development and validation of the Pain Sensitivity Questionnaire. *Pain*, *146*(1–2), 65–74.
- 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.
- Sarıdoğan, E. (2015). Endometriosis in teenagers. *Women's Health*, *11*(5), 705–709.
- Sethna, N. F., Meier, P. M., Zurakowski, D., & Berde, C. B. (2007). Cutaneous sensory abnormalities in children and adolescents with complex regional pain syndromes. *Pain*, *131*(1–2), 153–161.

- Simis, M., Reidler, J. S., Duarte Macea, D., Moreno Duarte, I., Wang, X., Lenkinski, R., Fregni, F. (2015). Investigation of central nervous system dysfunction in chronic pelvic pain using magnetic resonance spectroscopy and noninvasive brain stimulation. *Pain Practice: The Official Journal of World Institute of Pain*, 15(5), 423–432.
- 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.
- Sullivan, Bishop, S., & Pivik, J. (1995). The pain catastrophizing scale: development and validation. *Psychological Assessment*, 7(4), 524.
- Sullivan, M. (2009). *The Pain Catastrophizing Scale: User Manual*. Montreal, Quebec.
- Sullivan, M. J., Thorn, B., Haythornthwaite, J. A., Keefe, F., Martin, M., Bradley, L. A., & Lefebvre, J. C. (2001). Theoretical perspectives on the relation between catastrophizing and pain. *The Clinical Journal of Pain*, 17(1), 52–64.
- Sutton, C. J. G., Ewen, S. P., Whitelaw, N., & Haines, P. (1994). Prospective, randomized, double-blind, controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal, mild, and moderate endometriosis*. *Fertility and Sterility*, 62(4), 696–700.
- Talbot, N. L., Chapman, B., Conwell, Y., McCollum, K., Franus, N., Cotescu, S., & Duberstein, P. R. (2009). Childhood sexual abuse is associated with physical illness burden and functioning in psychiatric patients 50 years of age and older. *Psychosomatic Medicine*, 71(4), 417–422.
- Vercellini, P., Fedele, L., Arcaini, L., Bianchi, S., Rognoni, M. T., & Candiani, G. B. (1989). Laparoscopy in the diagnosis of chronic pelvic pain in adolescent women. *ResearchGate*, 34(10), 827–30.
- Vergnolle, N. (2008). Postinflammatory visceral sensitivity and pain mechanisms. *Neurogastroenterology and Motility: The Official Journal of the European Gastrointestinal Motility Society*, 20 Suppl 1, 73–80.
- Walker, S., Hopman, W. M., Harrison, M. B., Tripp, D., & VanDenKerkhof, E. G. (2012). Pain and psychological characteristics in women waiting for gynaecological surgery. *Journal of Obstetrics and Gynaecology Canada: JOGC = Journal D'obstetrique et Gynecologie Du Canada: JOGC*, 34(6), 543–551.

- Wall, P. D., Hubscher, C. H., & Berkley, K. J. (1993). Intraspinial modulation of neuronal responses to uterine and cervix stimulation in rat L1 and L6 dorsal horn. *Brain Research*, 622(1–2), 71–78.
- Ware, J. E., Kosinski, M., Dewey, J. E., & Gandek, B. (2000). *SF-36 health survey: manual and interpretation guide*. Quality Metric Inc.
- Whitaker, L. H. R., Reid, J., Choa, A., McFee, S., Seretny, M., Wilson, J., ... Horne, A. W. (2016). An Exploratory Study into Objective and Reported Characteristics of Neuropathic Pain in Women with Chronic Pelvic Pain. *PloS One*, 11(4), e0151950.
- Yamamoto, K., Mitsuhashi, Y., Takaike, T., Takase, K., Hoshiai, H., & Noda, K. (1997). Tubal endometriosis diagnosed within one month after menarche: a case report. *The Tohoku Journal of Experimental Medicine*, 181(3), 385–387.
- Yin, H., Yu, M., Cheng, H., Zhang, F., Gao, Y., Lin, J., Zhu, L. (2005). Beta-endorphin prevents collagen induced arthritis by neuroimmuno-regulation pathway. *Neuro Endocrinology Letters*, 26(6), 739–744.
- Youngster, M., Laufer, M. R., & Divasta, A. D. (2013). Endometriosis for the primary care physician. *Current Opinion in Pediatrics*, 25(4), 454–462.

CURRICULUM VITAE

