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The Interplay between Hormones and Irritable Bowel Disease

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THE INTERPLAY BETWEEN HORMONES AND IRRITABLE BOWEL DISEASE

by

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ABSTRACT

This thesis examines the underlying mechanisms causing the severe and often debilitating symptoms associated with both Irritable Bowel Syndrome and Inflammatory Bowel Disease. These disorders are characterized by, abdominal pain, bloating, constipation and diarrhea, and the symptoms are often intermittent. The variable onset and offset of symptoms suggests that periodic fluctuations in body state or signaling may play a role in the etiology and presentation of symptoms. This thesis proposes that the actions of the main intestinal hormones and their interactions with other hormones such as estrogen and progesterone may explain the oscillatory nature of the symptomatology. Spikes in the hormone progesterone may induce IBS-like symptoms such as cramping and constipation thereby representing a potential mediator of IBS symptoms. Evaluating the hormone progesterone's role in IBS and IBD may create a new target for therapeutic treatments. Moreover, hormonal-based therapy represents a potential means to treat the cause, rather than just the symptoms of IBS and IBD.

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LIST OF ABBREVIATIONS

ANS	Autonomic Nervous System
CCK	Cholecystokinin
FGID	Functional Gastrointestinal Disorder
GIP	Gastric Inhibitory Peptide
IBD	Irritable Bowel Disease
IBS	Irritable Bowel Syndrome
VIP	Vasoactive Inhibitory Peptide

INTRODUCTION

Irritable Bowel Syndrome, also known as IBS, is one of the many mysterious syndromes within the gastrointestinal internal medicine field. The National Institute of Health states that IBS has been termed a syndrome, not a disease, because the symptoms, although chronic, seem to come and go (http://digestive.niddk.nih.gov/ddiseases/pubs/ibs_ez/, 2011). IBS, a syndrome of the bowel, has been termed a "functional disorder" by many physicians due to the fact that a clearly defined pathophysiological cause, mechanism or substrate has not yet been acknowledged (Oberndorff-Klein, 2004). Because IBS cannot be diagnosed based upon biological parameters, IBS is diagnosed by the presence of specific symptoms including, but not limited to, abdominal pain, bloating, diarrhea, cramping and constipation (Oberndorff-Klein, 2004).

The Mayo Clinic, one of the leading facilities in gastroenterology research, defines IBS as a disorder of the large intestine that causes a constellation of symptoms that often vary from patient to patient (http://www.mayoclinic.com/health/irritable-bowel-syndrome/DS00106/, 2012). Because many of these symptoms can often resemble those of other diseases, the diagnosis of IBS can prove to be quite difficult. Physicians diagnose IBS through an exclusion criterion by asking a series of questions, and sometimes performing procedures, such as stool tests, flexible sigmoidoscopies, colonoscopies and endoscopies. Once it is evident that no organic pathology exists and that the patient

is not suffering from one of the many diseases of the gastrointestinal tract such as Crohn's disease, colonic diverticulosis or ulcerative colitis, a diagnosis of IBS may be introduced (Bommelaer et al., 2004). In this way, IBS is a diagnosis by exclusion.

CAUSE

Currently there is no accepted theory behind the cause of IBS. Researchers have begun to study multiple hypotheses but defined conclusions have not yet been drawn. The National Institute of Health recognizes five potential causes that are currently being studied by researchers. These causes include, brain-gut signaling problems, colon muscle dysfunction, hypersensitive nerves in the gut, bacterial infections, and the overgrowth of intestinal bacteria (http://digestive.niddk.nih.gov/ddiseases/pubs/ibs_ez/. 2011). Brain-gut signal problems are being studied in relation to their effect on bowel habits and abdominal pain and discomfort. Colon muscles may dysfunction. When the muscles of the colon contract too much they can cause diarrhea and abdominal cramping. When the muscles of the colon do not contract sufficiently, constipation can ensue.. Hypersensitive nerves located in the gut may directly cause the abdominal pain or discomfort when stool is present, an effect increased by the presence of stress or anxiety. Bacterial infections such as gastroenteritis have also been noted to initiate the symptoms of IBS. And lastly, the NIH denotes the overgrowth of intestinal bacteria, such as flora, as being a potential causative agent (http://digestive.niddk.nih.gov/ddiseases/pubs/ibs_ez/, 2011).

It is clear that physicians and scientists alike have not yet narrowed down what causes this debilitating syndrome. This thesis attempts to dive deeper into the potential basis of syndrome and the possible reasons for the erratic fluctuations in symptoms seen in many of the patients suffering from IBS.

Features and Symptoms

In order to fully understand what causes IBS, it is important to understand how this syndrome is diagnosed, and what factors play a role in the difficulties for providers to come to a clear and concrete diagnosis. Because this syndrome does not have a defined pathophysiological marker, symptoms serve as the primary means to diagnose IBS (Corazziari, 2004). Based on the Rome Criteria, the gold-standard and most-used criteria for IBS, a diagnosis of IBS is concluded when the patients symptoms have been present for at least six months, abdominal pain or discomfort has been present for at least three days every month for the last three months, and that the abdominal pain or discomfort has two or three specific defining features (Corazziari, 2004). The specific features are as follows: the pain or discomfort lessens following a bowel movement, there is a change in how the patient has a bowel movement following the pain or discomfort, and following the pain or discomfort there is a change in stool appearance (http://digestive.niddk.nih.gov/ddiseases/pubs/ibs_ez/, 2011).

The difficulty in diagnosing IBS, a syndrome usually diagnosed by exclusion, has led to the overall complexity of diagnosing and treating this syndrome. The

general failure of a unified approach from the three major criteria has attributed to the differences in diagnoses. Enrico Corazziari ascribed the failure in diagnosing IBS to the differences between the Rome I, Rome II and Manning criteria (Corazziari, 2004). Table 1 lists the three criteria for diagnosing IBS: the Manning Criteria, the Rome I Criteria, and the Rome II Criteria (Corazziari 2004):[1]

Table 1. Diagnostic Criteria of IBS

Table 1. Diagnostic criteria of the irritable bowel syndrome.

Manning criteria	Rome I criteria	Rome II criteria
Abdominal pain that is relieved with a bowel movement Pain associated with looser stools Pain associated with more frequent stools	Continuous or recurrent symptoms of: Abdominal pain, relieved with defecation, or associated with a change in frequency or consistency of stool;	Continuous or recurrent symptoms for at least 12 weeks in the past 12 months Abdominal pain or discomfort that has two out three features: relieved with defecation, or associated with a change in onset frequency or consistency of stool
Sensation of incomplete evacuation	And Two or more of the following, at least on one-fourth of the occasions or days	Symptoms that cumulatively support the diagnosis of IBS Altered stool frequency > 3evac day; < 3evac/week
Passage of mucus	Altered stool frequency	Altered stool form (lumpy/hard or loose/watery)
Abdominal distension	Altered stool form (hard or loose/watery)	Altered stool passage (straining/or urgency, feeling of incomplete evacuation)
	Altered stool passage (straining or urgency, feeling of incomplete evacuation), Passage of mucus Bloating or feeling of abdominal distension	Passage of mucus Bloating or feeling of abdominal distension

[1] Corazziari, E. (2044). Definition and epidemiology of functional gastrointestinal disorders. Best Practice & Research Clinical Gastroenterology. Vol 18(4), 613-631.

Table 1 shows that although these three different criteria have overlapping features, there are substantial disparities in each one of the three descriptions of the same syndrome. The lack of a consensus adds confusion to the definition of Irritable Bowel Syndrome and what makes it different from other gastrointestinal disorders. Without a clear definition of IBS, it is difficult for providers to appropriately diagnose and treat the disease. While this chart represents insight into why IBS has been such a source of confusion for both patients and providers in today's society, it is only one example of the complexities behind the IBS story.

Along with the differing criterion used for diagnosis, the Rome Criteria classify the functional gastrointestinal disorders (FGID) into subcategories: oesophageal, gastroduodenal, bowel, biliary, anorectal, and abdominal pain (Corazziari. 2004). Because many people often have overlapping disorders, diagnosing FGIDs by classifying them into specific subcategories may cause providers to disregard patients who have overlapping FGIDs (Corazziari. 2004).

According to The Mayo Clinic, the symptoms of IBS include, but are not limited to, cramping, abdominal pain, bloating, gas, diarrhea, constipation and mucus in the stool (http://www.mayoclinic.com/health/irritable-bowel-syndrome/DS00106/, 2011). The Mayo Clinic addresses the fact that although IBS is a chronic condition, the signs and symptoms associated with this disorder often fluctuate. The Mayo Clinic defines IBS is a multifactorial syndrome brought upon by a combination of both environmental and genetic determinants. The heterogeneous nature of this disease adds to its complexity, creating a vast disparity in symptoms

between patients. Without a clear indication as to why the signs and symptoms, can at times, worsen, or even dramatically improve to an almost undetectable level, it becomes almost impossible for providers to implement an effective treatment plan.

IBS versus IBD

Inflammatory Bowel Disease is comprised of two diseases, Crohn's disease and ulcerative colitis (Abraham et al., 2009). Similar to IBS, the exact mechanism underlying these diseases is not fully understood but current evidence suggests that these diseases result from inflammatory responses to intestinal microbes (Abraham et al., 2009). A diagnosis of Crohn's disease occurs through colonoscopy when inflammation, often discontinuous, is found in the colon, ileum, and any other regions of the intestine (Abraham et al., 2009). Ulcerative colitis is also diagnosed via colonoscopy and usually involves inflammation, often in an interrupted pattern, in the rectum and other parts of the colon (Abraham et al. 2009). It is unclear how prominent the role of genetic factors are in these two diseases but current evidence suggests that there may be a stronger genetic linkage to Crohn's disease than ulcerative colitis (Abraham et al., 2009). Similar to IBS, many therapies for inflammatory bowel disease have failed to provide relief from many of the symptoms associated with both Crohn's disease and ulcerative colitis (Abraham et al., 2009) Many medications for inflammatory bowel disease such as anti-TNF-alpha monoclonal antibodies are directed towards decreasing the inflammation but do not

alleviate many of the symptoms associated with these diseases such as abdominal pain, bloating, constipation, diarrhea and rectal bleeding (Abraham et al., 2009).

Irritable Bowel Syndrome has in the past been deemed a purely psychological disorder, but recent studies have contradicted this once accepted theory (Lam et al., 2011). Post-infectious IBS, that is, IBS that is triggered by a gastrointestinal infection, such as gastroenteritis, has been shown to have much more in common with Inflammatory Bowel Disease than previously thought. Robin Spiller and Ching Lam of the Digestive Research Center at Nottingham University have proposed that IBS should be examined with a holistic approach, just as has been done in the past for IBD (Lam et al., 2011). IBS overlaps with IBD in four main areas: genetic factors, gut permeability dysfunctions and gut responses to microbiota, and symptoms (Lam et al., 2011). IBS, a syndrome that has been deemed completely psychological due to the lack of pathological findings and markers, has recently been gaining recognition as a disease that may be conquerable due to its stark similarities with IBD.

One of the main similarities between IBS and IBD is the correlation between stress on the body and the symptomatic flare-ups (Lam et al., 2011). Flare-ups are periods of time when the painful symptoms of either IBS or IBD are at their peak. Depending on the individual, flare-ups can last anywhere from ten minutes to a few hours. It is the unknown mechanism behind the peaks and plateaus in symptoms that occur in IBS that have physicians and scientists alike perplexed. Spiller and

Lam offer the idea that the mechanism behind these flare-ups in both IBD and post-infectious IBS may be closely related if not the same (Lam et al., 2011).

Stress, one of the main instigators, may activate flare-ups through a mast cell (MC) mechanism. Animal studies have shown that mast cells are activated and released by stress (Lam et al., 2011). Researchers at the University of Nottingham have connected this idea to humans, stating that stress causes the "activation of the hypothalamic pituitary axis, increased tissue myeloperoxidase and increased luminal T lymphocytes along with increased piecemeal degranulation of MCs and increased luminal tryptase which correlated with increased jejunal permeability." (Lam et al., 2011).

Although a mechanism involving mast cells may just be just one of the many possible ways symptom fluctuations are activated, looking at increases and decreases of GI permeability may shine light onto what really causes the symptomatic fluctuations. Because IBD is more established in its pathogenesis, examining the commonalities between IBD and IBS offers the possibility that there are joint mechanistic similarities. The idea that IBD and IBS are more related in mechanism and pathology than previously thought may provide leverage to a better understanding of IBS.

Quality of Life

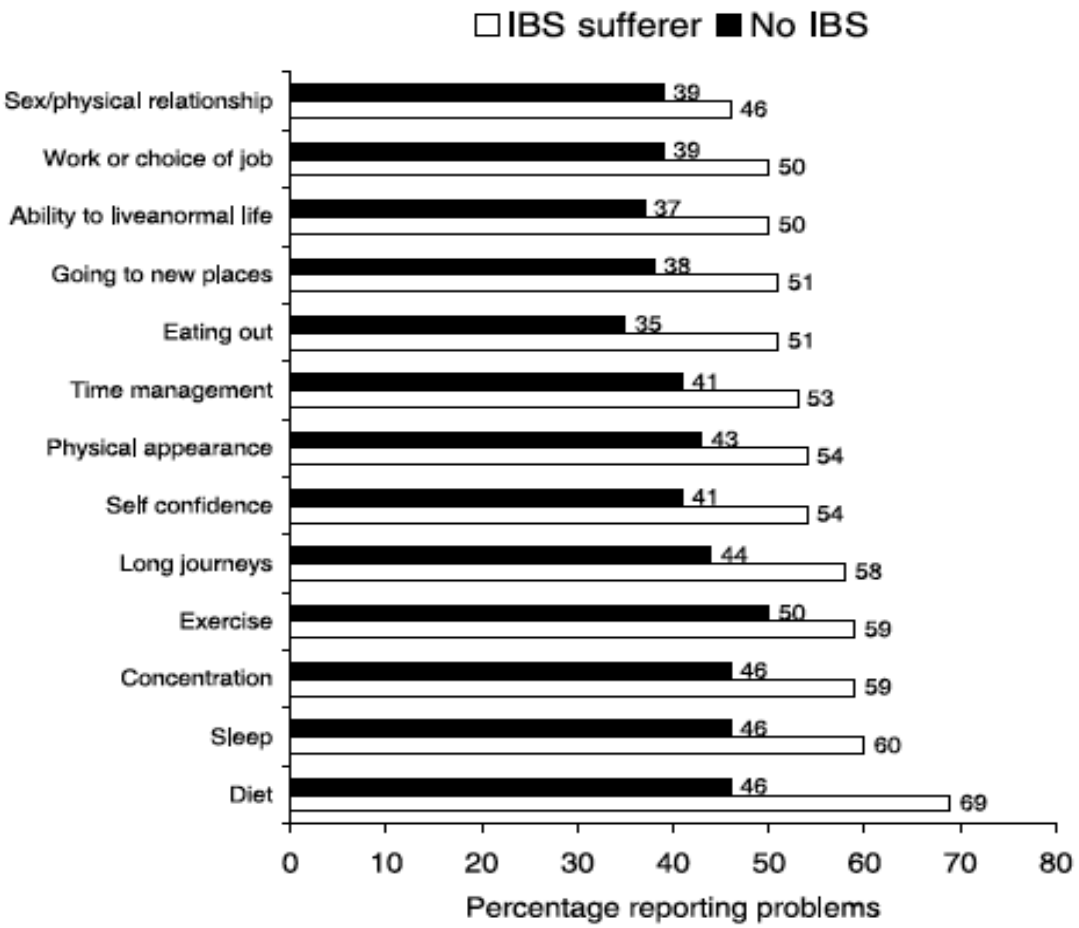
IBS negatively impacts quality of life. The quality of life of someone suffering from IBS is similar to that of someone suffering from another chronic condition such as severe migraines, asthma or gastro-oesophageal reflux disease (Quigley et al., 2006). The tremendous burden on quality of life in a patient suffering from IBS is in need of much more attention and evaluation.

In an international survey including 40,000 subjects conducted by Hungin et al., at the University of Durham, 78% of subjects suffering from IBS reported that their IBS symptoms significantly affected their lives and general well being (Hungin et al., 2002).

In addition, irritable bowel syndrome sufferers reported having more sickness days off work in the previous 12 months: overall, they spent 3.9 days in bed (corresponding figure for non-sufferers, 2.7 days), 5.5 days sick off work (3.1 days), 8.4 days seeing a doctor or nurse (5.2 days) and 10.2 days when work activities had to be cut short (4.8 days). Of those who had formally been diagnosed with irritable bowel syndrome, 96% had shared information about their problem with others, but only 10% had told their employer. Of those formally diagnosed, 60% felt that their condition would be with them for life and that they had a real medical condition (Hungin et al., 2002).

The hindrance of IBS on the lives of sufferers is substantial and not vastly recognized by either physicians or society. Figure 1 depicts the impact IBS can have on various areas of life (Hungin et al., 2002)[2]:

Figure 1. Percentage of IBS Sufferers Reporting



[2] Hungin APS, Whorwell PJ, Tack J, Mearins F. (2002). The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Alimentary Pharmacology and Therapeutics. Vol 17, 643-650.

Both sexual and physical relationships, working, traveling, eating, sleeping and exercise are a few of the many areas that are affected in IBS patients. These negative impacts and disturbances of daily activities are responsible for the drastic drop in quality of life. In order to reduce the number of people that go undiagnosed, and for physicians and scientists to focus on researching and creating effective treatments, IBS must start to be recognized as a real and serious medical condition.

IBS On Its Own

It is important for physicians to not just diagnose IBS by ruling out other similar, yet life-threatening, diseases such as colorectal cancer, but by looking at IBS as an entity in and of itself. The next challenge is for physicians to provide a way to manage this very complicated disorder. "Although pharmacological treatments for IBS are available in the EU, robust clinical evidence of their efficacy and safety are lacking" (Quigley et al., 2006). Most of the treatments available for IBS concentrate on relieving the symptoms, often exacerbating the syndrome as a whole. A more mindful approach to creating an effective treatment plan for this syndrome would be to focus on the possible underlying causes that give way to the symptoms. In this way, providers could focus on treating the cause instead of the current approach, which aims to dampen the intensely fluctuating symptoms without concern for their future impact.

Treatments

The NIH claims that although Irritable Bowel Syndrome can be painful, often disrupting daily activities, the signs and symptoms of IBS do not damage the gastrointestinal tract (http://digestive.niddk.nih.gov/ddiseases/pubs/ibs_ez/, 2011). Often, patients suffering from IBS are dismissed by their physicians due to the lack of knowledge and scientific validation surrounding the underlying mechanisms of this syndrome (Occhipinto et al., 2012). Based on current theories that IBS may be related to IBD much more than previously thought there may be some concern that IBS may not just be a purely symptomatic, benign syndrome, but instead, a syndrome that may lead to damaging results down the line such as increased risk for colorectal cancers (Lam et al., 2011).

In order to present novel therapies for patients suffering from severe IBS, one must first take a look at the current therapeutic options. Because this syndrome is not understood on the pathologic level, the therapies prescribed are usually targeted to relieve individual symptoms (Camilleri et al., 2009). Current therapies usually target one of four main areas of symptomatic concern: constipation, diarrhea, gas and bloating, and pain (Camilleri et al., 2009). Symptoms of constipation, diarrhea, and gas and bloating can all be targeted via various therapies, each having three lines of therapeutic agents. The first line of therapeutic agents for constipation relief includes fiber capsules, laxatives and stool softeners. The second line of therapeutic agents includes stimulant laxatives such as Bisacodyl and Lubiprostone, while the third line of agents includes Linaclotide and serotonin

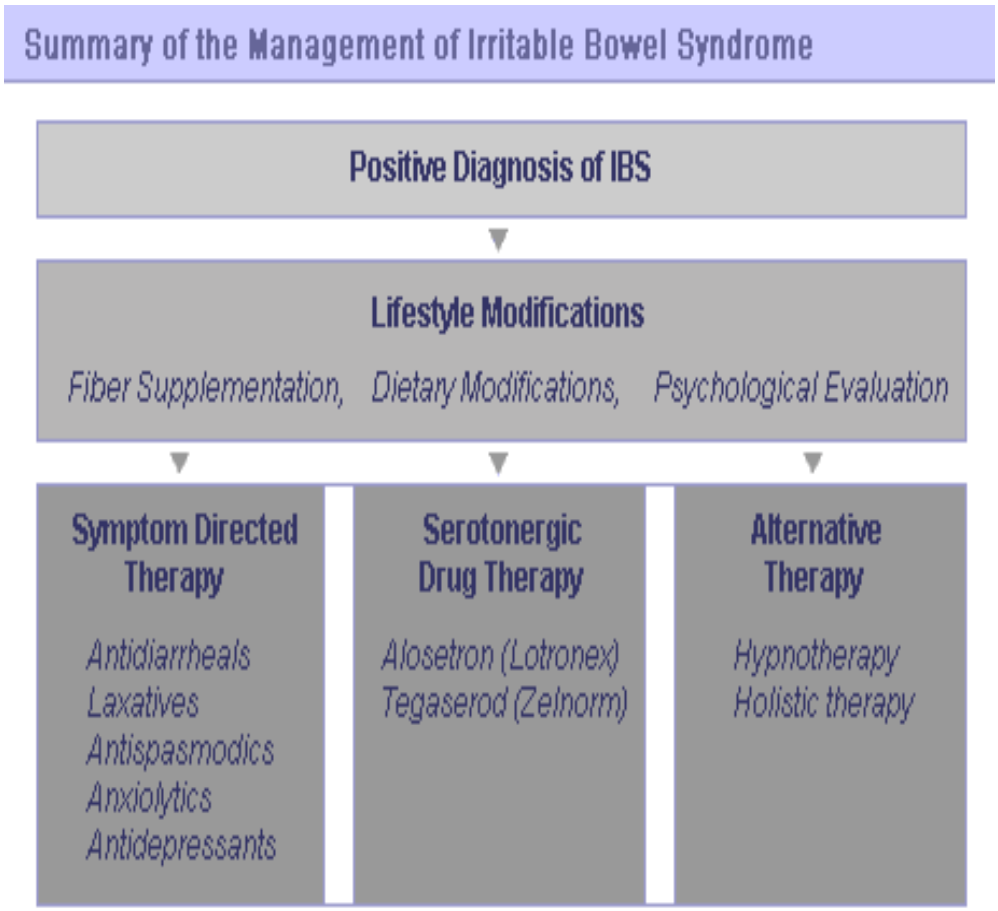
(5-HT) agonists (Camilleri et al., 2009). Diarrhea can be treated by Loperamide and Diphenoxylate which are part of the first line treatment, and also by Alosetron, bile acid sequestrant and Clonidine, a group of smooth muscle antispasmodics (Camilleri et al., 2009). The symptoms of gas and bloating can also be treated by two lines of therapies, but these treatments overlap treatments for many of the other symptoms. The first line of treatment for gas and bloating is the same method that treats the constipation while the second line of treatment is through the use of probiotics, whose effectiveness has yet to be fully evaluated (Camilleri et al., 2009).

While the symptoms of constipation, diarrhea, and gas and bloating seem to have defined therapeutic agents, the most devastating symptom of pain lacks effective therapeutic agents. Those suffering from IBS pain are often prescribed antidepressants and antipsychotics such as Anxiolytic, Duloxetine, Clonidine and Pregabalin (Camilleri et al., 2009). These drugs are prescribed to symptomatic IBS patients because the drugs affect anxiety and mood disorders and therefore can sometimes have positive effects on the visceral sensation of the gut (Camilleri et al., 2009). Although these drugs are often prescribed to patients suffering from painful IBS, their efficacy has yet to be proven (Camilleri et al., 2009). The National Institute of Diabetes and Digestive and Kidney Disorders also sites psychological therapy, such as talk therapy and gut-direct hypnotherapy as potential therapies to reduce IBS pain (http://digestive.niddk.nih.gov/ddiseases/pubs/ibs_ez/, 2011).

Johns Hopkins Medicine Section of Gastroenterology and Hepatology represent the symptomatic management of IBS through the following chart that

describes the various therapies available for patients diagnosed with IBS (http://www.hopkinsgi.org/GDL_Disease.aspx?CurrentUDV=31&GDL_Cat_ID=AF793A59B73642CB9E1FE79D2B9FC358&GDL_Disease_ID=F5E21D6B-A88E-44F9-900F-7E295C50D38B, 2001-2013)[3]:

Figure 2. Summary of the Management of Irritable



[3] John Hopkins Medicine of Gastroenterology and Hepatology. (2001-2013). Irritable bowel syndrome (IBS): therapy. http://www.hopkinsgi.org/GDL_Disease.aspx?CurrentUDV=31&GDL_Cat_ID=AF793A59B73642CB9E1FE79D2B9FC358&GDL_Disease_ID=F5E21D6B-A88E-44F9-900F-7E295C50D38B.

Figure 2 depicts the tremendous emphasis that is placed on therapies that take a symptomatic approach. Lifestyle modifications, psychosocial therapies and symptom directed therapies are all treatments that focus on alleviating the symptoms of IBS rather than the causes. Serotonergic drug therapy such as Alosetron and Tegaserod are novel therapies for IBS that are currently being studied and act to reduce visceral sensitivity and gust sensation while also slowing colonic transport and motility (http://www.hopkinsgi.org/GDL_Disease.aspx?CurrentUDV=31&GDL_Cat_ID=AF793A59B73642CB9E1FE79D2B9FC358&GDL_Disease_ID=F5E21D6B-A88E-44F9-900F-7E295C50D38B, 2001-2013). These drugs mark the beginning of treatment therapies that target some of the potential causal mechanisms, and not just the symptoms, associated with IBS.

Although these therapies may relieve painful IBS symptoms for periods of time, they are therapies created primarily for different diseases, and can carry a high risk of causing serious adverse effects. Their long-term effectiveness has yet to be evaluated, and these drugs should be taken with extreme caution. It is important to attempt to develop therapies that target the underlying mechanisms of painful IBS rather than just targeting the symptoms (Trinkley et al., 2010) so that novel therapies are created that are causally directed and based on targeting the mechanism of the disorder (Anderson et al., 2011).

Epidemiology

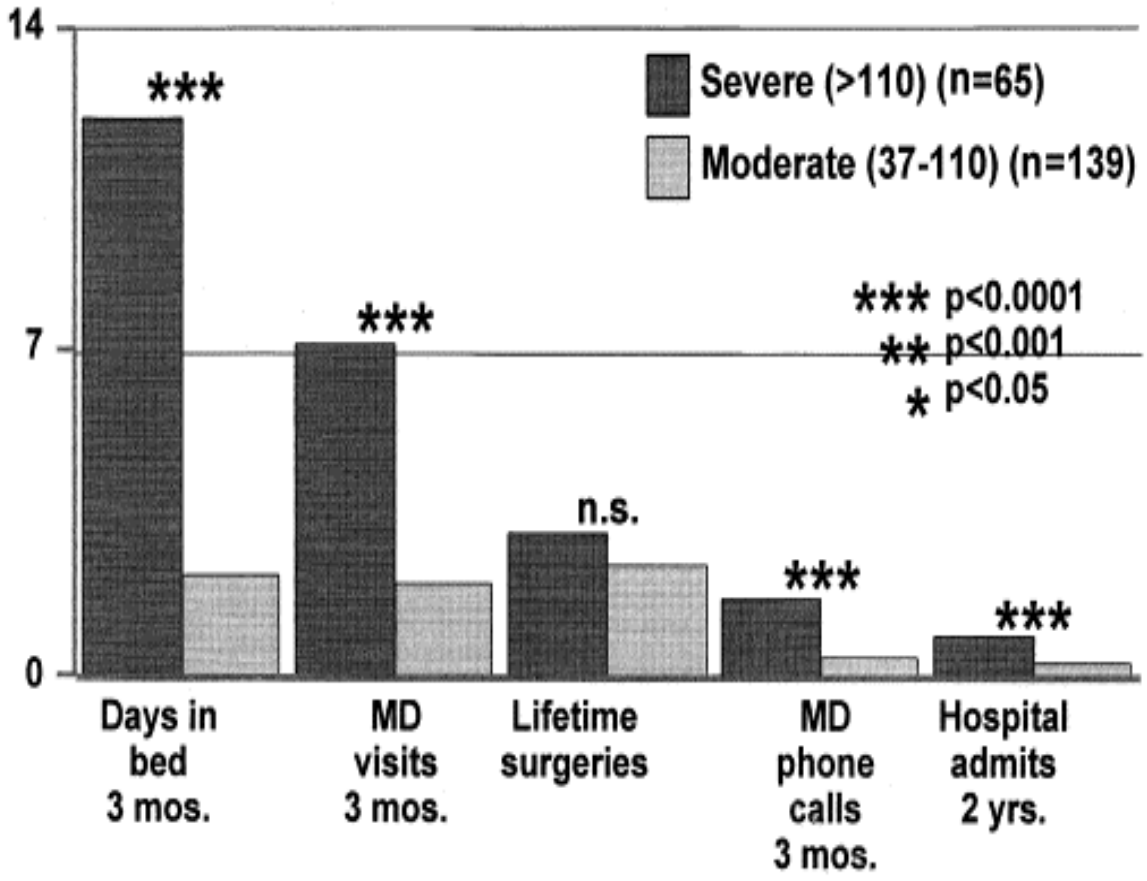
Dr. Sarah Payne from the University of Bristol in the United Kingdom estimated that nearly forty percent of the population in the United Kingdom suffers from many of the symptoms of irritable bowel disease (Payne, 2004). The high prevalence of IBS was also found in developing countries with a documented forty-four percent of people in Nigeria and twenty-five percent in Bangladesh suffering from IBS-type symptoms (Payne, 2004). A recent primary care study in the United Kingdom concluded that on average, a primary care general practitioner would see eight IBS patients every week (Oberndorff-Klein, 2004).

K.E Trinkley et al., from the Ohio State University stated that IBS, although mostly undiagnosed, might affect nearly 15% of the population in The United States (Trinkley et al., 2010). Trinkley also states that IBS is responsible for three to five million office visits a year, adding up to 45 billion dollars in healthcare every year. The reason these costs skyrocket is due to the inability of healthcare professionals to effectively manage the symptoms of IBS (Trinkley et al., 2010).

Figure 3 compares health-care utilization between patients with severe IBS versus patients with moderate IBS. It is clear from this chart that patients with severe IBS utilize health care much more frequently due to their painful and disruptive symptoms as compared to patients with moderate IBS (Drossman, 1999)[4]:

[4] Drossman, D. (1999). Do psychosocial factors define symptom severity and patients status in irritable bowel syndrome? American Journal of Medicine. Vol 107(5), 41-50.

Figure 3. Health Care Utilization of IBS Sufferers



Patients self diagnosed their IBS as either severe or moderate and answered five quantitative questions regarding the amount of days they spend in bed over a three month period of time, the amount of physician visits they attend in a three month period of time, the amount of surgeries they have had over their lifetime due to their IBS condition, the amount of phone calls they made to their physician over a three month period of time and the number of hospital admissions due to their condition over a two year period (Drossman, 1999). The amount of days in bed, visits and

phone calls to physicians, lifetime surgeries, and hospital admissions, were significant and extremely high for patients suffering from severe IBS. The inability to treat the painful symptoms of IBS effectively and efficiently can take a toll on not just the healthcare system, but society as a whole (Drossman, 1999). Without effective treatment for IBS, these patients' symptoms, their care and quality of life is sure to suffer.

Gender Disparities

In order to begin to understand the pathology and mechanisms behind the painful and disruptive symptoms of IBS, it is necessary to look at the population of people that are affected the most.

IBS does not seem to be related to ethnicity or race (Chang et al., 2006), but appears to be correlated with gender. Women are two times more likely than men to be diagnosed and treated for IBS. A community based study from Northern India showed the prevalence of IBS in men versus women (Makharia, 2011)[5]:

[5] Makharia GK, Verma AK, Amarchand R, Goswarmi A, Singh P, Agnihotri A, Suhail F, Krishnan A. (2011). Prevalence of irritable bowel syndrome: a community based study from northern India. Journal of Neurogastroenterology and Motility, 17(1):82-7

Figure 4. Prevalence of IBS in Men Versus Women

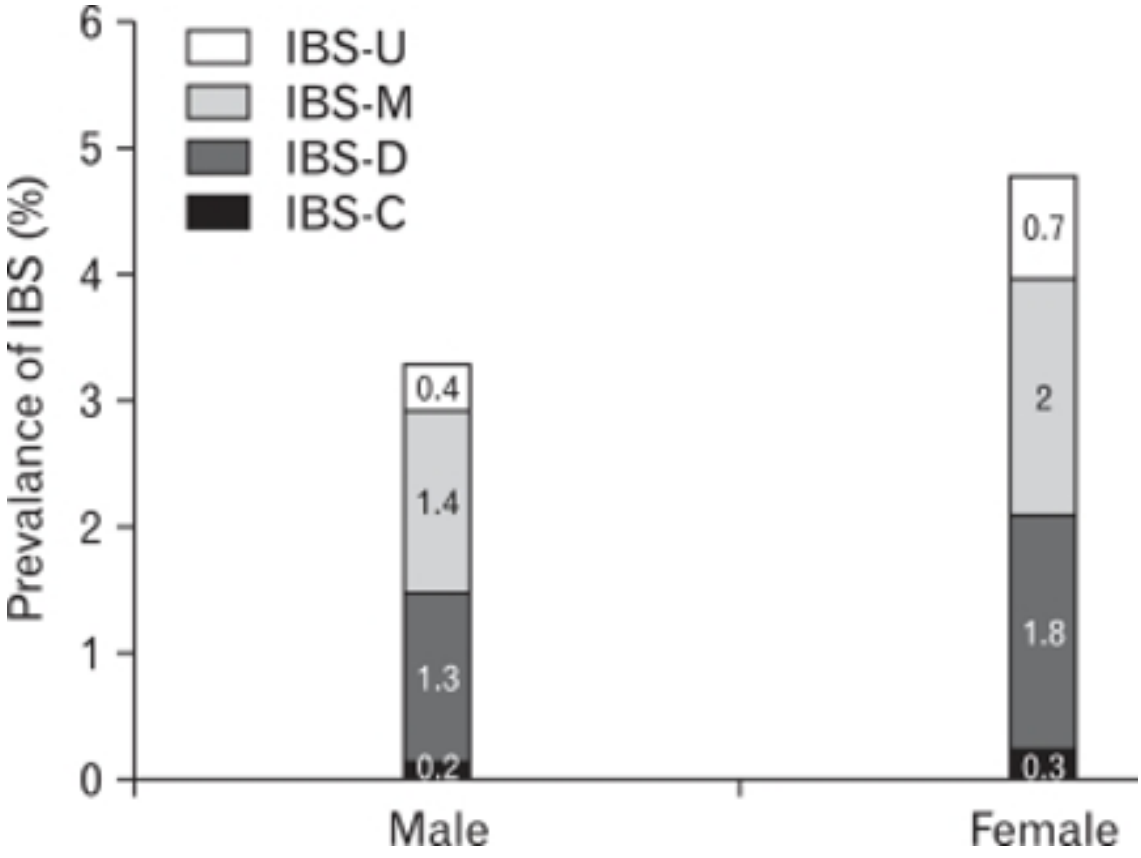


Figure 4 shows the drastic distinction between the numbers of men and women that suffer from IBS even when sampling just a small community in Northern India. IBS-D is characterized as the man symptom being diarrhea, IBS-C is characterized as the main symptom being constipation, IBS-M is characterized as a mix of symptoms, and IBS-U is characterized as alternating symptoms (Makharia, 2011). This study showed that the women from the community had a significantly higher prevalence of IBS as compared to the men, but that there were no significant differences in the prevalence of various IBS subtypes (IBS-U, IBS-C, IBS-D, IBS-M) between the men and women (Makharia, 2011).

Not only do women suffer more from IBS than men, but women with IBS are more likely to report dysmenorrhea and premenstrual distress syndrome as compared to women who do not suffer from IBS (Heitkemper et al., 2006). This may suggest that there is a connection between the pain experienced during IBS and the hormones that surge throughout the menstrual cycle.

One of the reasons that a higher percentage of women are diagnosed with IBS as compared to men is because women are more likely to seek provider services and care for functional gastrointestinal conditions (Heitkemper et al., 2008). Another reason why IBS is disproportionately diagnosed in women as compared to men is due to the potential effect of the menstrual cycle on IBS symptoms such as transit and motility. The hormone progesterone, a main player in the menstrual cycle hormone fluctuation patterns, acts in an inhibitory manner on the smooth muscle of the colon (Gill et al., 1985). Women suffering from IBS are more likely to seek services for constipation, while men are more likely to seek services for diarrhea (Heitkemper et al., 2008). These findings suggest that the spike in progesterone seen a few weeks before menses may be influencing or even exacerbating the symptom of constipation.

Ovarian hormones such as estrogen and progesterone may alter gut motility and visceral hypersensitivity, causing or worsening the painful symptoms often documented in IBS (Heitkemper et al., 2006). Although the gender related differences seen in IBS are likely multifactorial involving environmental, psychological, genetic and biological factors, the event of gonadal maturation

coinciding with the onset of painful IBS symptoms suggests that these two events are not independent (Heitkemper et al., 2008).

Overall there is a great deal of emerging evidence that suggests that the menstrual cycle may play a major role in the generation and onset of IBS symptoms. The next section will attempt to examine the relationship between the menstrual cycle and the onset of IBS symptoms in women.

The Menstrual Cycle and Symptoms of IBS

The gender difference associated with IBS often begins during early puberty, increases during the adult years and then slowly levels off. The prevalence in IBS in older men compared to older women does not seem to be different (Heitkemper et al., 2008). This fluctuation in IBS symptoms mirrors that of a woman's menstrual cycle. Menses begins at puberty and are halted when women enter their fifties and sixties during menopause. The drastic symptomatic discrepancy between men and women appears during the period of time when women begin to ovulate, and ceases when women enter into menopause.

The following figures show how the painful IBS symptoms are amplified during the time of a woman's menstrual cycle (Giamberardino et al., 1997)[6]:

[6] Giamberardino MA, Berkley KJ, Lezzi S, et al. (1997). Pain threshold variations in somatic wall tissues as a function of menstrual cycle, segmental site and tissue depth in non-dysmenorrheic women, dysmenorrheic women and men. Pain. Vol 71(2), 187-197.

Figure 5. Abdominal Pain Fluctuations During Menses

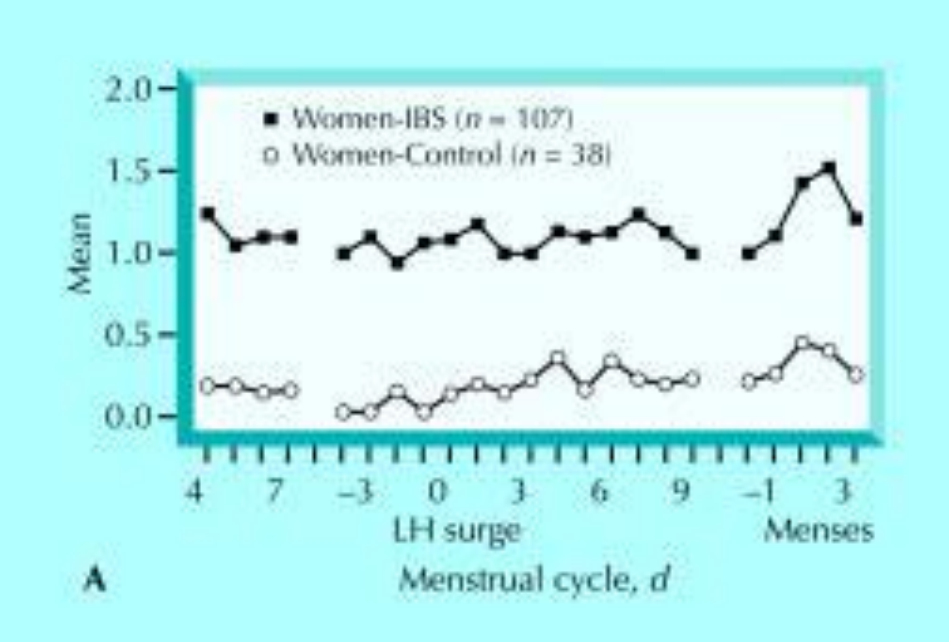


Figure 6. Bloating Symptom Fluctuations During

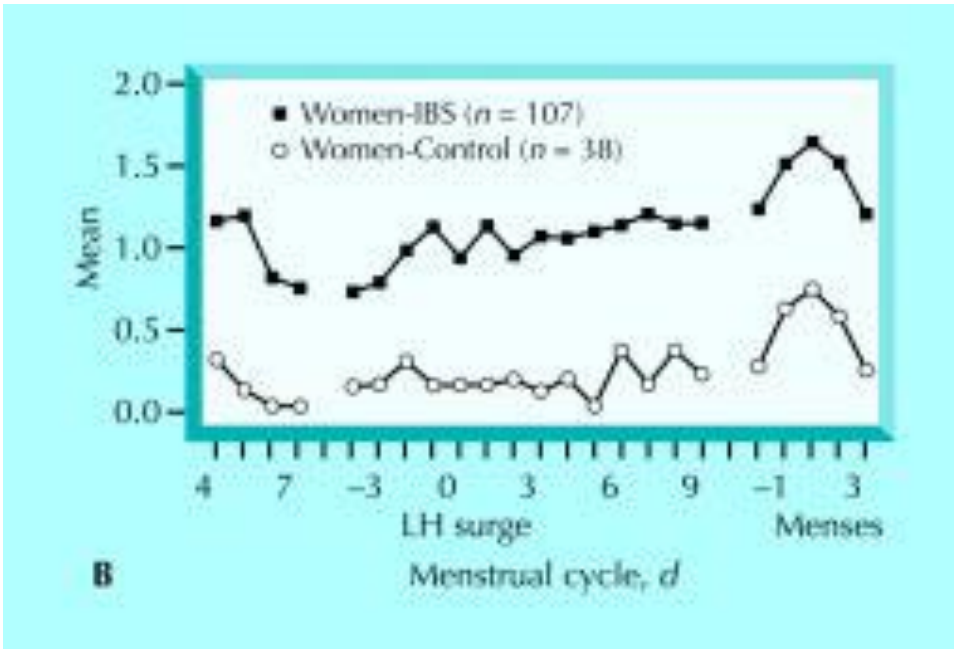


Figure 7. Constipation Symptom Fluctuations During Menses

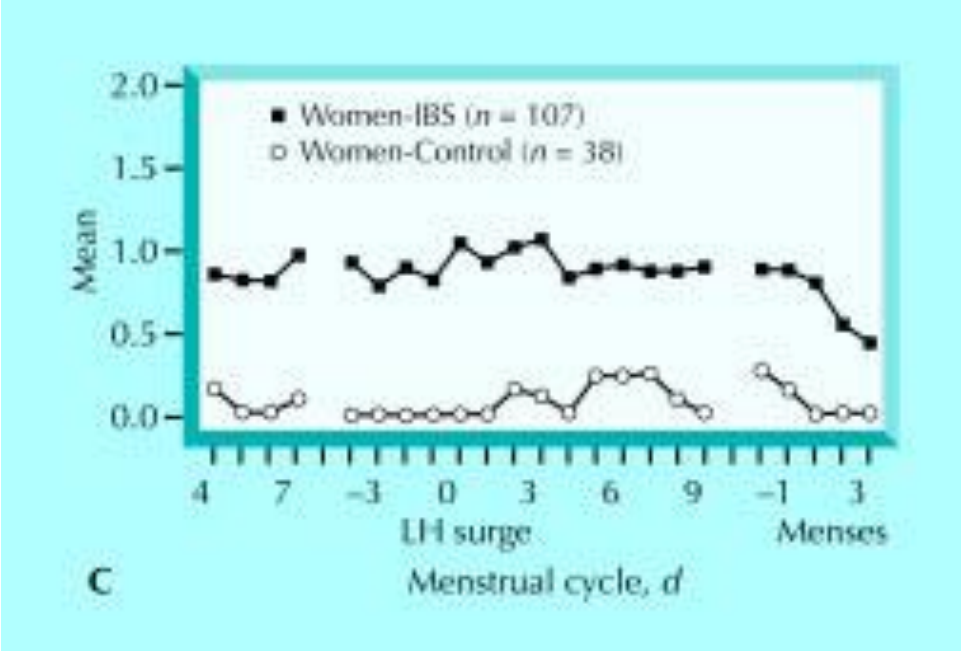
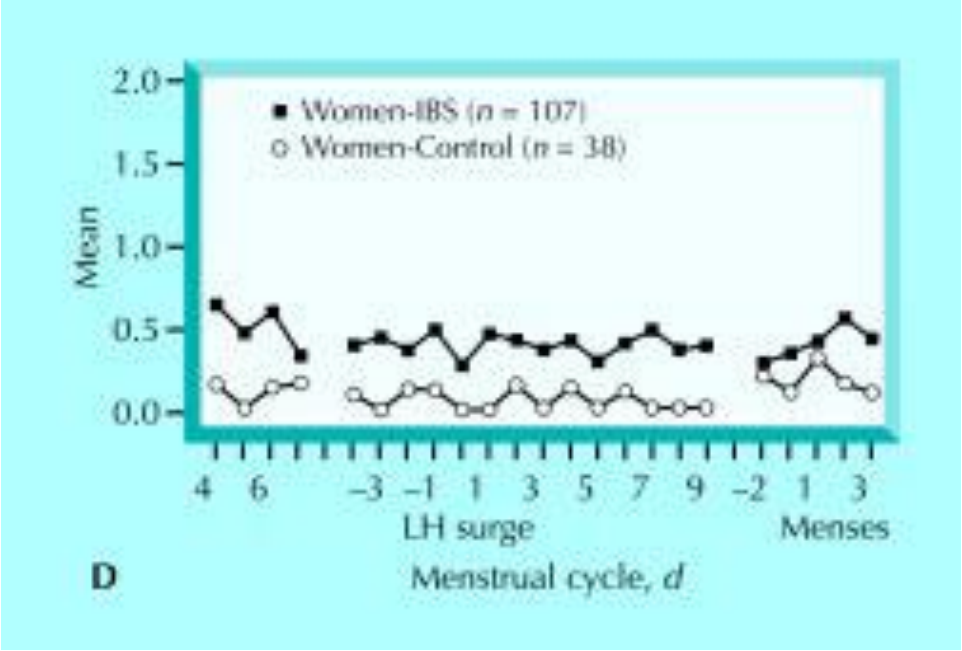


Figure 8. Diarrhea Symptom Fluctuations During Menses



These figures compare the influence of menstrual hormones on pain related symptoms between women who suffer from IBS and women who do not. Figure 5 compares abdominal pain between the two cohorts of women. Figure 6 compares the symptom of bloating between the two cohorts. Figure 6 compares the level of constipation experienced by the two cohorts of women, and Figure 7 compares the level of diarrhea experienced during the menstrual cycle between the two cohorts of women. The mean abdominal pain, bloating, and constipation that both cohorts of women experience follow the same fluctuation patterns but the women suffering from IBS show a dramatically elevated mean pain level as compared to the control women. This study suggested that the symptom of diarrhea in women suffering from IBS actually decreased during the period of time following the LH surge when progesterone levels are high (Giamberardino et al., 1997). This would suggest that progesterone plays a role in further inducing abdominal pain and bloating by exacerbating constipation and inhibiting diarrhea (Giamberardino et al., 1997). These studies suggest that estrogen and progesterone, the predominant hormones that are elevated following the LH surge of the menstrual cycle, may play very large roles in modulating the painful symptoms experienced in women suffering from IBS (Heitkemper et al., 2001).

With the onset of menses comes the steep increase in estrogen and progesterone, possibly responsible for the severe symptomatic disparity seen amongst men and women during this period of time. Heitkemper et al., discusses, "The variability in reproductive hormones across the menstrual cycle as well as the

decrease in ovarian function at menopause may serve as important factors influencing GI motility and visceral sensitivity." This suggests that GI motility and visceral sensitivity, which are key contributors to the symptomatic painful IBS experience by those suffering from IBS, may be influenced by the hormone level fluctuation that occurs during a woman's menstrual cycle (Heitkemper et al., 2008).

Objective

The purpose of this thesis is to delve deeper into the mechanisms behind Irritable Bowel Disease and propose various hormones as possible key players behind the mystery of symptom fluctuations and gender disparities in those suffering from IBS. Understanding the interplay between specific hormones and the symptoms associated with IBS will allow physicians and scientists to create novel therapies to target the mechanism behind the fluctuations rather than just taking a superficial approach and relieving the symptoms instead of the underlying problems. This paper will discuss in detail the gastrointestinal and ovarian hormones, their interplay, and ways in which these hormones may be significantly influencing the symptom fluctuations of IBS. The intended effect of this information is to enhance our knowledge of the gastrointestinal environment that gives way to IBS, allowing us to create therapies through future research that may alleviate the underlying mechanisms that cause the painful symptoms associated with IBS,

thereby greatly increasing the quality of life for millions of individuals across the world.

Introducing The Gastrointestinal Hormones

The functions of the gastrointestinal tract are regulated by endocrine, paracrine and neurocrine hormones (Johnson, 2001). While the gastrointestinal tract may not be the first area of the body that comes to mind when one thinks about hormones, the gastrointestinal tract is actually home to many hormones (Preston, 1985). Although there are a multitude of hormones that play roles in the gastrointestinal tract, this thesis will focus on five main gastrointestinal hormones. Secretin, gastrin, cholecystokinin, gastric inhibitory peptide, and motilin are five hormones that act primarily in the gastrointestinal tract, and whose actions may contribute to some of the many symptoms associated with IBS. Looking at these hormones and better understanding their applications throughout the gut may provide us with a better overall picture in what mediators may be influencing gut dysfunction; and whether or not they may play a role in many of the symptoms of IBS.

Secretin was the first gut hormone to be discovered in 1902 by Bayliss and Starling (Johnson, 2001). Secretin is a hormone dispelled by hydrochloric acid in the duodenal mucosa and has the unique ability to stimulate pancreatic bicarbonate and fluid secretion (Johnson, 2001). Gastrin, the second gut hormone to be

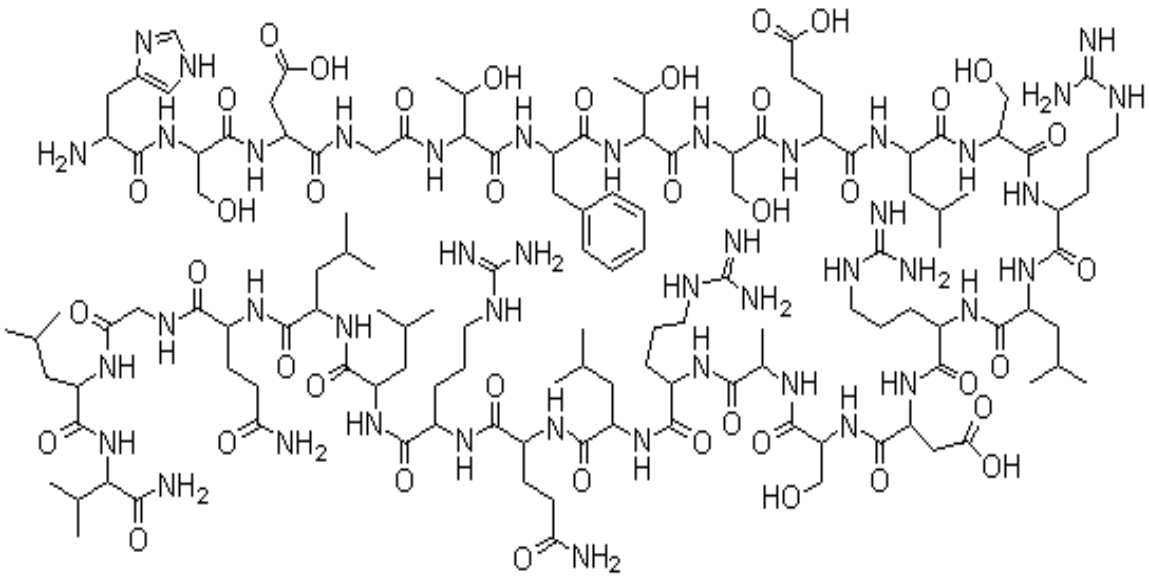
discovered, aids in the digestion and absorption of food in the stomach by stimulating secretory cells (Rai, 2012). The presence of fat in the intestine stimulates the hormone CCK (cholecystokinin) to initiate the contraction of the gall bladder (Johnson, 2001). CCK is released from the small intestine and stimulates pancreatic enzyme secretions (Rai, 2012). Gastric inhibitory peptide (GIP) is another hormone of the gut that is released from the intestinal mucosa in response to fat and glucose to inhibit gastric secretion (Johnson, 2001). The last hormone that we will discuss is motilin, a crucial hormone within the gastrointestinal system. Motilin, a 22-amino acid peptide that primarily resides in the upper part of the small intestine is the main hormone responsible for gastrointestinal motility (XH, 1993). Motilin is also one of the hormones that is responsible for further proving the connection between the brain and the gut, because the actions of motilin are driven by neural control (XH, 1993).

Secretin

Secretin, the polypeptide hormone that is responsible for pancreatic bicarbonate and fluid secretion has the following molecular structure (http://www.chemblink.com/products/17034-35-4.htm)[8]:

[7] ChemBlink. (2013). Online database for chemicals around the world. Secretin. http://www.chemblink.com/products/17034-35-4.htm.

Figure 9. The Molecular Structure of Secretin



H-His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Asp-Ser-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2

Secretin, as shown above in figure 9, has 27 amino acids and is part of a group of peptides that include the homologous structures of vasoactive intestinal peptide (VIP), GIP and glucagon (Johnson, 2001). Secretin does not have one active segment, but instead, the entire molecule is needed in order for secretin to function properly (Johnson, 2001). Because GIP and VIP have homologous structures to secretin, many of their actions are similar, overlap and act in identical manners (Johnson, 2001). Both secretin and GIP inhibit acid secretions but while GIP only stimulates insulin release, secretin has many stimulating effects (Pfaffl, 2003). Secretin stimulates pancreatic bicarbonate secretion, bile bicarbonate secretion, and pancreatic growth (Johnson, 2001).

While certain hormones such as gastrin and motilin increase the contractions of the stomach, secretin and GIP inhibit these contractions. The caudad region of the stomach that has contractions that increase in force and velocity as they approach the gastroduodenal junction (Hellstrom, 2009). Secretin also has inhibiting effects on the contractions of the small intestine but its exact role in the motility of the small intestine has yet to be fully evaluated (Pfaffl, 2003). The inhibition or stimulation of contractions of the small intestine may be a factor in intestinal motility dysfunction.

Gastrin

Unlike secretin, which requires the entire structure to be effective, the four C-terminal amino acids of gastrin are the critical functional portion (Johnson, 2001). Gastrin's five C-terminal amino acids are identical to those of CCK, and therefore, these two hormones can activate each other's receptors (Johnson, 2001). While secretin, CCK, GIP, and motilin are mostly concentrated in the duodenum and jejunum, gastrin is primarily active in the antral and duodenal mucosa (Johnson, 2001). Gastrin along with the hormone motilin are the only gut hormones that are released strictly by neural stimulation (Johnson, 2001). The primary actions of gastrin are to stimulate the release of gastric acid secretion and to stimulate mucosal growth (Hellstrom, 2009). Gastrin also plays a role in the contractions of the smooth muscle that lines the stomach and the intestine. Whereas secretin plays

a role in inhibiting the smooth muscle contractions, gastrin and motilin increase the contractions (Johnson, 2001).

There are many factors that control the motility of the small and large intestines. Interstitial smooth muscle cells, enteric nerves, extrinsic nerves, and circulating or locally released chemicals are some of the many factors that may contribute to the increases and decreases in intestinal motility (Hellstrom, 2009). The gastroileal reflex, the term that describes the relaxation of the sphincter and the increase in contractility of the ileum following a meal, is mediated and stimulated primarily by both gastrin and CCK (Johnson, 2001). Many of the other gut hormones such as somatostatin, secretin and GIP all inhibit either gastrin release or acid secretion (Johnson, 2001).

Gastrin is a hormone released into the circulation following a meal along with other hormones such as secretin and CCK (Johnson, 2001). The release of gastrin induces a multitude of digestive organ functions such as propulsive contractions and increases in splanchnic blood flow (Johnson, LR. 2001). Gastrin's structure is almost identical to the structure of CCK (Rai et al., 2012). Figure 10 shows the structure of both Gastrin and CCK, two hormones that belong to the same gastrointestinal family of peptides that regulate functions in both the gastrointestinal tract and the central nervous system (Rai et al., 2012)[9]:

[9] Rai R, Chandra V, Tewari M, Kumar M, Shukla H. (2012). Cholecystokinin and gastrin receptors targeting in gastrointestinal cancer. Surgical Oncology. Vol 21:4, 281-292.

Figure 10. Molecular Structure of CCK and Gastrin

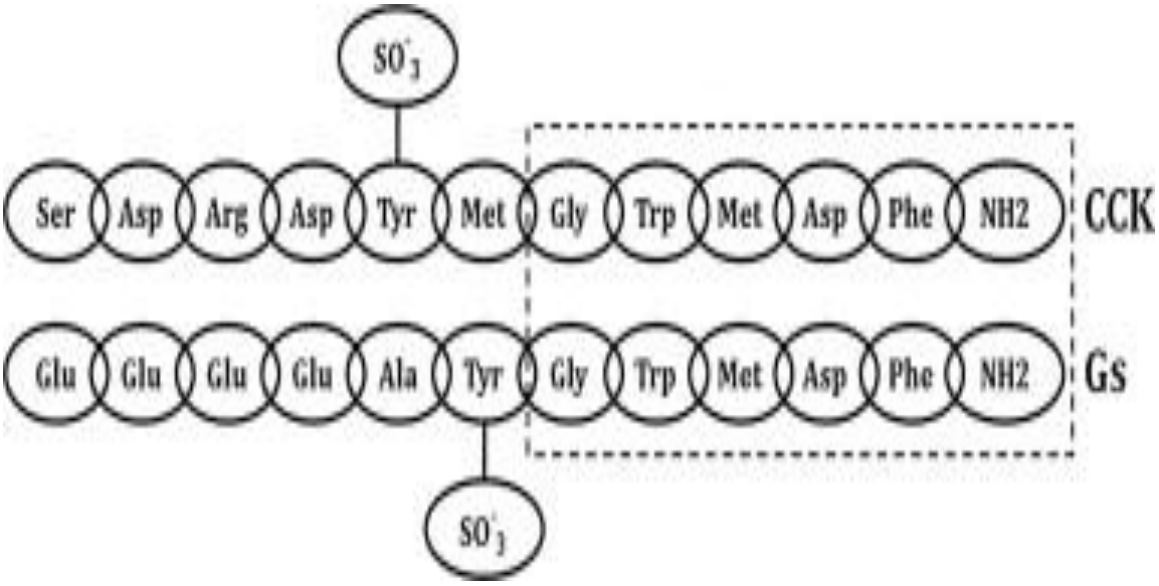


Figure 10 depicts how closely related Gastrin and CCK are structurally. Although these hormones take on different roles throughout the body, they share the same C-terminal pentapeptide sequence (Rai et al., 2012). As previously states, Gastrin, the hormone produced by the endocrine G-cells of the gastric antrum, stimulates acid secretion in the stomach, the exocrine pancreas and the large and small intestinal mucosa growth, while CCK, synthesized in the small intestine and cerebral neurons, has a variety of functions that vary from those of Gastrin (Rai et al., 2012).

CCK

Shortly after the discovery of Gastrin, the hormone that initiates gallbladder contractions was discovered in 1928 (Johnson, 2001). This hormone was named cholecystokinin because of its primary function, and that it is the presence of fat in

the intestine that stimulates CCK to begin acting (Johnson, 2001). Because CCK and Gastrin are so similar structurally, they have the unique ability to activate each other's receptors (Johnson, 2001). That is, CCK can activate the receptors for acid secretion and Gastrin can activate the receptors for gallbladder contractions (Johnson, 2001). Along with the contraction of the gallbladder, CCK stimulates pancreatic secretion, intestinal motility, cell growth, gene expression and protein synthesis (Rai et al., 2012). Because CCK functions in a variety of ways it has receptors all over the body such as the gallbladder smooth muscles, gastric mucosa cells, pancreatic acinar cells, stomach and other areas in both the central and peripheral nervous systems (Rai et al., 2012). CCK has also been demonstrated to stimulate the release of other hormones such as glucagon while also inhibiting gastric emptying (Johnson, 2001). CCK, along with gastrin, have been shown to cause increases in colonic motility, and CCK has also been shown to increase rectal sensitivity to pain during periods of distension (van der Schaar et al., 2013). Along with the increased sensitivity to pain, CCK has been presented as a hormone that may be involved in the symptoms associated with IBS. Evidence has suggested that abnormal colonic motility, due to its generation of increased intraluminal pressure, can lead to diverticular formation (Johnson, 2001). Because CCK plays a large role in the transit motility just as gastrin does, there may be a correlation between the functions and effects of CCK, gastrin, secretin, which inhibits intestinal motility, and the symptoms associated with IBS (Johnson, 2001).

Gastric Inhibitory Peptide

Gastric Inhibitory Peptide (GIP) is one of the major gastrointestinal hormones. Released from the intestinal mucosa in response to fat and glucose, GIP acts to inhibit gastric secretion and stimulate insulin release GIP also acts as an antagonist to CCK by inhibiting intestinal motility and gastric emptying (Johnson, 2001). While some hormones like gastrin and motilin act to increase gastric contractions; GIP, secretin and the hormone somatostatin act to inhibit gastric contractions (Preston, 1985). Similar to GIP is the gut peptide hormone GLP-1, also known as glucagon like peptide hormone (Hellstrom, 2009). A study conducted in 2009 in Sweden by Hellstrom et al., looked at incretin hormones such as GLP-1 and their effect on gut motility and symptomatic IBS (Hellstrom, 2009). The study concluded that GLP-1 acted as an inhibitory hormone on small bowel motility via vagal pathways in both controls and patients suffering from IBS (Hellstrom, 2009). The study concluded that incretin hormones, such as GIP and GLP-1, may be of clinical significance to understanding many of the gut motility disorders such as IBS (Hellstrom, 2009).

MOTILIN

Motilin, discovered in the 1970s, is a small intestine hormone composed of 22 amino acids arranged in a linear fashion (Johnson, 2001). This hormone plays a crucial role in the gut. The cyclical release of motilin is responsible for upper gastrointestinal motility (Johnson, 2001). Motilin is a major hormone in the

connection between the central nervous system and the peripheral nervous system. Motilin's release, just like gastrin, is under neurological control, and is responsible for the interdigestive migrating myoelectric complex that moves through the stomach and small bowel every ninety minutes (Miller et al., 1999).

Phase III of the migrating myoelectric complex is the most active phase of the cycle. During this phase, bursts of contractions stimulated by motilin originate in the antrum and the duodenum and then migrate distally (Miller et al., 1999). Although motilin is under neurological control, it acts directly on the smooth muscle of the intestine (Miller et al., 1999). The actions of motilin are so potent and directed that motilin now represents the strongest hormonal stimulus for gastric contractions (Miller et al., 1999). This finding opens up a world of causes and treatments for patients suffering from gastrointestinal motility disorders (Miller et al., 1999). High levels of motilin have been associated with abnormal increases of gut activity and researchers have found abnormally high levels of motilin in patients suffering from IBS (Palsson et al., 2013).

Concluding the Gastrointestinal Hormones

These give gut hormones, secretin, gastrin, GIP, CCK and motilin provide a much deeper understanding as to what is controlling many of the intestinal functions. We will now look into the role some of the ovarian hormones might play throughout the intestine, as well as take a deeper look into many of their interactions with other hormones. Keep in mind the importance each gut hormone,

secretin, gastrin, CCK, GIP and motilin, and their potential effects on the underlying mechanisms associated with IBS symptoms such as constipation, diarrhea, bloating, and abdominal pain.

The Ovarian Hormones

As previously stated, women are twice as likely to suffer from IBS than men (Chang et al., 2006). This disparity could be attributed to one of the key differences between men and women: their gonadal hormones. IBS symptoms in women tend to emerge at the time of gonadal maturation, when the follicle stimulating hormone (FSH), luteinizing hormone (LH), estrogen and progesterone begin to be excreted throughout the body at much higher levels (Heitkemper et al., 2008). In order to better understand how these sex hormones play a role in symptomatic IBS, it is important to take a deeper look at the menstrual cycle and the effects of the ovarian hormones, estrogen and progesterone, on gastrointestinal symptoms. Studies have been performed suggesting that women diagnosed with IBS and IBD suffer from cyclic pain fluctuations, suggesting that female gonadal hormones play a role in the modulation of painful signal processing (Ji et al., 2008).

The average length of a woman's menstrual cycle is 28 days. During this period of time, the four main female sex hormones, FSH, LH, estrogen and progesterone rise and fall in a cyclical manner. Figure 11 shows the hormonal

fluctuations that occur throughout the menstrual cycle (Smith, 2009)[10]:

Figure 11. Hormone Fluctuations throughout the Menstrual Cycle

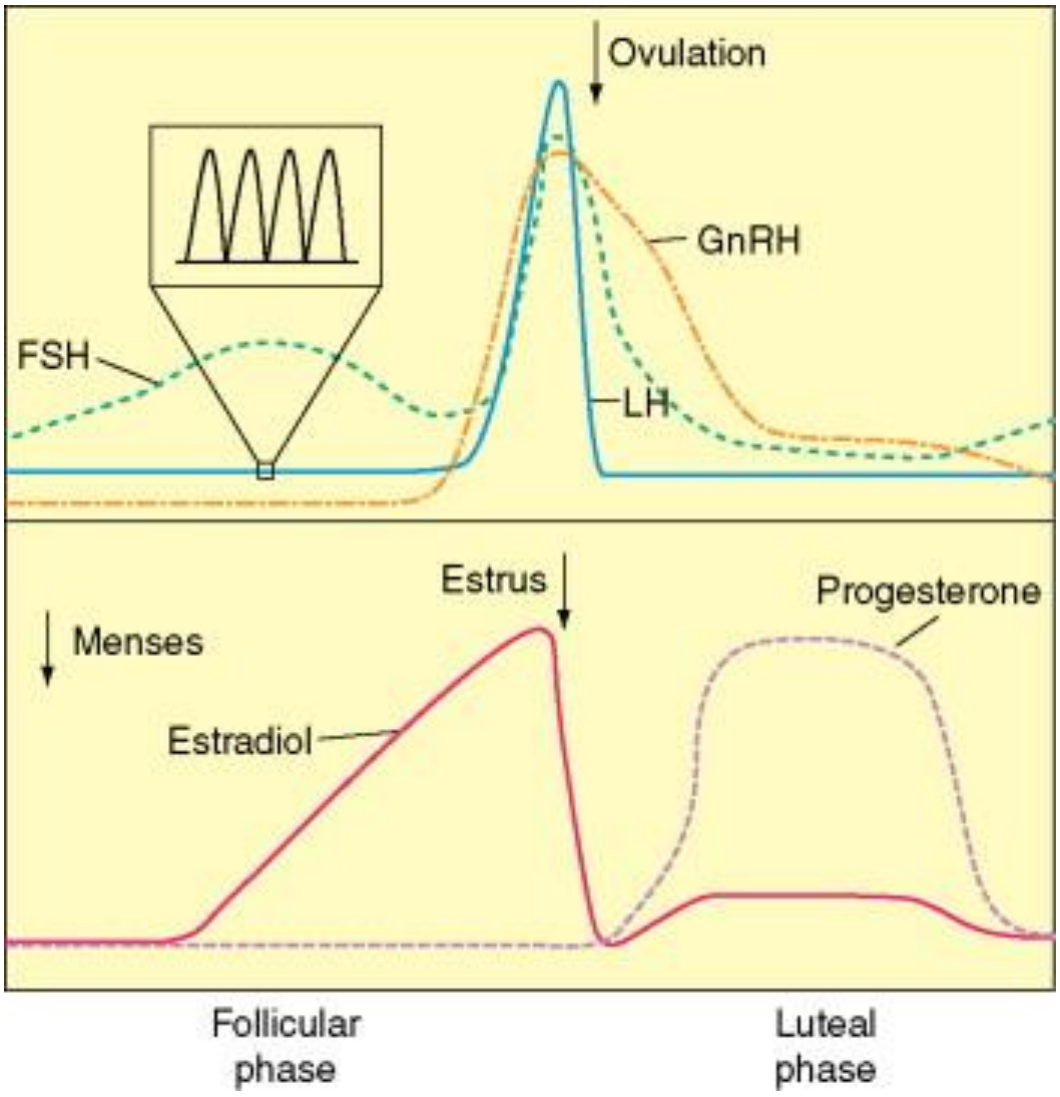


Figure 11 represents the pattern of hormonal fluctuations that occurs throughout the menstrual cycle. Levels of LH and FSH remain fairly low and then spike around day fourteen of the menstrual cycle so that ovulation can occur (Smith, 2009).

[10] Smith MS. (2009). Estrus and menstrual cycles: neuroendocrine control. Encyclopedia of Neuroscience. Pages 1-5.

Levels of estradiol and estrus, forms of the ovarian sex hormone estrogen, are elevated during the follicular phase and drop dramatically once ovulation has occurred (Smith, 2009). Progesterone, the other very important ovarian hormone other than estrogen, is the only hormone in the above schematic that has increased levels during the luteal phase of the menstrual cycle (Smith, 2009). Once the menstrual cycle occurs, the levels of progesterone drop dramatically, rising again in a cyclical manner following ovulation during the luteal phase (Smith, 2009).

Both estrogen and progesterone, secreted from the ovaries, do not just affect cells directly around the ovaries (Nelson et al., 2001). These hormones are released into the blood stream, allowing them to act on various organs and cells by either inhibiting or stimulating their functions (Palsson et al., 2013). There are many other sites throughout both men and women that estrogen and progesterone can modulate, such as those within the vascular endothelial and smooth muscle cells (Nelson et al., 2001).

Ovarian Hormone Fluctuations and Gastrointestinal Symptoms

Receptors for both progesterone and estrogen have been found on gastrointestinal cells (Palsson et al., 2013). This finding suggests that the ovarian hormones are designed to influence the gastrointestinal tract, and that the fluctuations in IBS symptoms that seem to correlate to the cyclic hormonal fluctuations during the menstrual cycle, are not a coincidence (Palsson et al., 2013).

A study conducted by Jackson et al. published in the Journal of Gastroenterology found that female IBS patients suffered from greater sensitivity to rectal distention during the perimenstrual period, the period of time two weeks prior to the start of menses (Jackson et al., 1997). Other studies have found that the IBS symptom of bloating tends to be exacerbated during the luteal phase, suggesting that progesterone, the only hormone prominent during this phase, may play a role in modulating the symptoms of IBS (Palsson et al., 2013).

Congruent with these findings, a study conducted by Hapidou et al., found that women have a much lower pain threshold during the luteal phase, when progesterone is elevated, as compared to the follicular phase (Hapidou et al., 1988). Balloon distention studies have also found that women who suffer from IBS have cyclical increases in gut pain sensitivity, further suggesting a hormonal role in the fluctuations of IBS symptom severity (Palsson et al., 2013). Gastrointestinal transit time has been found to be markedly slow during the luteal phase as compared to the follicular phase in women suffering from IBS (Heitkemper et al., 2001). Pre-menopausal women have also been shown to have slower gastric emptying as compared to post-menopausal emptying, suggesting that estrogen and/or progesterone plays a role in inhibiting gastric emptying (Heitkemper et al., 2001).

In addition to the influence estrogen and progesterone have been found to have over the visceral pain experienced by women suffering from IBS, changes in autonomic nervous system function and/or balance have been found in approximately 33% of patients suffering from IBS. The autonomic nervous system

(ANS) is comprised of the parasympathetic nervous system; which includes the ovarian hormones estrogen and progesterone, and sympathetic nervous system. The ovarian hormones estrogen and progesterone are mediated and controlled by the autonomic nervous system, and patients suffering from severe IBS symptoms may also be suffering from an imbalance in efferent fibers to the gut (Heitkemper et al., 2001). These ANS imbalances may be contributing to alterations in gastrointestinal symptoms such as gut motility, constipation, diarrhea, muscle tone, secretion, visceral sensitivity and luminal distention (Heitkemper et al., 2001). The association between ANS imbalances and IBS symptoms provides further evidence that hormonal fluctuations play a large part in the symptomatic fluctuations seen in patients suffering from IBS.

IBS Symptoms During Pregnancy and Menopause

Pregnancy provides another model in which to look at the effects of ovarian hormones on IBS symptoms. Progesterone, a hormone that is usually only elevated during the luteal phase of the menstrual cycle in women, plays a large role during pregnancy. Progesterone, a hormone essential for a healthy pregnancy, begins to rise dramatically once pregnancy occurs and remains elevated during the course of pregnancy (Druckmann et al., 2005). Progesterone works to build the endometrial lining, an essential step for the implantation of the fertilized egg (Druckmann et al., 2005). The elevated progesterone levels during pregnancy are congruent with the

exacerbated gastrointestinal symptoms that occur in IBS patient throughout the course of pregnancy.

In a study examining the effect of progesterone on colonic smooth muscle in canines showed that progesterone reduced the force of contractions in both the longitudinally and circulatory oriented strips of smooth muscle, as well as the frequency of contractions in the longitudinally oriented strips of smooth muscle (Gill et al., 1985). Constipation is one of the most common complaints during pregnancy, in which women experience symptoms consisting of infrequent defecation, hard and/or pellet like stool, and excessive straining that can often lead to external hemorrhoids (Prather, 2004). Progesterone, shown to exert an inhibitory effect on colonic smooth muscle in the study focusing on colonic smooth muscle (Gill et al., 1985), could account for many of the IBS-like symptoms such as cramping and constipation, known to be exacerbated during pregnancy, a time when the hormone progesterone is abnormally elevated in women.

Baron et al. concluded that the changes occurring throughout the gastrointestinal tract during pregnancy, such as alterations in gastric motor function and decreases in small-bowel colonic transit, causing bloating and constipation, are in response to the elevated levels of hormones (Baron et al., 1993). This finding further links the ovarian hormones, particularly progesterone, to the exacerbated gastrointestinal symptoms; suggesting that the hormone progesterone plays a large role in modulating, stimulating, and enhancing the gastrointestinal symptoms of IBS.

Constipation, a very serious and clinical problem associated with slow colonic transit, affects close to 20% of the US population and is seen primarily within the female population (Gonenne at al., 2006). These symptoms often begin during at menarche, when women experience their first menstrual period, and are relieved once menstruation begins when levels of progesterone and estradiol levels dramatically drop resulting in looser stools (Gonenne at al., 2006). Pregnancy, a period of time when these two hormones, progesterone and estradiol are markedly elevated, also represents a period of time during when women experience exacerbated levels of constipation and cramping (Gonenne at al., 2006). Women have been shown to have prolonged orocecal transit time, a measure of the gastric and small intestine transit speed, during the luteal phase of the menstrual cycle as well as the second and third trimesters of pregnancy, times when progesterone levels are greatly elevated (Gonenne at al., 2006).

While an increase in IBS-like symptoms has been shown to occur during the luteal phase of the menstrual cycle and during pregnancy when progesterone levels are high, a decline in IBS-like symptoms has been indicated following menopause, when the ovaries' production of estrogen and progesterone decrease dramatically (Palsson et al., 2013).

The Interplay Between the Gut Hormones and Progesterone

Although there has been little research done on the role the gut hormones secretin, gastrin, CCK, gastric inhibitory peptide, and motilin might play in IBS, there is reason to believe that the oscillating levels of these hormones, as well as their interactions with progesterone, may explain the fluctuating symptoms of IBS.

A study focusing on the effect of female sex hormone supplementation and withdrawal on colonic transit time within a postmenopausal female population suggested that the upregulation of progesterone is associated with G protein receptor disorders (Gonenne et al., 2006). G proteins, proteins associated with the contractions and relaxations of smooth muscles, are known to play a major role in patients suffering from severe constipation (Gonenne et al., 2006). The overexpression of progesterone receptors in conjunction with elevated levels of progesterone causes an upregulation of G proteins, increasing the hormone vasoactive inhibitory peptide (VIP), a prominent hormone responsible for inhibiting smooth muscle contractions (Cheng et al., 2010). The link between progesterone, G proteins and VIP may provide a possible mechanism for progesterone's role as a possible constipation inducer (Gonenne et al., 2006).

CCK and motilin are both hormones that initiate gastrointestinal activity and contractions following a meal (Palsson et al., 2013). Following a meal it is normal to have CCK and motilin initiate intestinal contractions, but many people who suffer from IBS have exacerbated symptoms of constipation and cramping following a meal, suggesting that there may be something else affecting CCK and motilin

(Palsson et al., 2013). A study comparing the levels of motilin and the levels of progesterone found in pregnant women during the first, second and third trimesters as well as post-birth, found that progesterone and motilin levels were indirectly proportional (Qiu, 1993). Plasma motilin and serum progesterone levels were measured in a 180 women throughout pregnancy as well as 3-5 days following delivery (Qiu, 1993). A negative correlation was found between these two hormones, when progesterone levels were elevated during the late stages of pregnancy, levels of motilin were decreased (Qiu, 1993). When levels of progesterone dropped immediately following delivery, levels of motilin were markedly increased (Qiu, 1993). This study suggests that progesterone has a dominant and inhibitory effect on motilin. High levels of motilin and CCK have also been found in patients suffering from IBS, suggesting that the increased levels of these hormones are a compensatory mechanism within the gut attempting to overcome the inhibitory affects progesterone plays on intestinal activity (Palsson et al., 2013).

It has been previously suggested that altered levels of gut hormones may play a role in the symptoms associated with functional gastrointestinal disorders (Preston et al., 1985). This paper suggests that it is the hormone progesterone that influences these altering levels. A study looking at motilin, pancreatic polypeptide and gastrin concentrations in relation to progesterone fluctuations in forty patients with functional bowel disease found a significant correlation between the fluctuations in the hormone progesterone to those of the intestinal tract (Preston et

al., 1985). This study found that the patients who experienced constipation and slow transit time had much lower levels of motilin, levels that correspond to increases in levels of progesterone (Preston et al., 1985). Progesterone has also been suggested as a possible gastrin inhibitor, and patients from this study with low levels of gastrin were found to have markedly increased symptoms of constipation, further elaborating on progesterone's role as an inducer, causing fluctuations in the various gut hormones; hormones that could very well be causing many of the symptoms associated with painful IBS (Preston et al., 1985).

Discussion

Irritable Bowel Syndrome, one of the most confusing and variable functional bowel disorders, has become an extremely burdensome syndrome in medicine. Because IBS cannot be diagnosed based upon biological parameters, IBS is now diagnosed by the presence of specific symptoms (Oberndorff-Klein, 2004), an often tumultuous guessing game that leaves many physicians bewildered and patients without answers. Because many of these symptoms can often resemble those of other diseases, the diagnosis of IBS can prove to be quite difficult.

Diagnosing IBS now occurs based on exclusion criteria, much due to the fact that no clear or defined cause has been found. The National Institute of Health recognizes six potential causes that are currently being studied by researchers. The potential causes of IBS include, brain-gut signaling problems, colon muscle

dysfunction, hypersensitive nerves in the gut, bacterial infections, and the overgrowth of intestinal bacteria (http://digestive.niddk.nih.gov/ddiseases/pubs/ibs_ez/. 2011). This thesis has attempted to create a model based on hormone fluctuations in both the intestinal tract and throughout the systemic system. This model focuses on hormone fluctuations in relation to some of the many symptoms of IBS. Based on the Rome Criteria, the gold-standard and must used criteria for IBS, a diagnosis of IBS is proposed when the patient's symptoms have been present for at least six months, abdominal pain or discomfort has been present for at least three days every month for the last three months, and that the abdominal pain or discomfort has two or three specific defining features (Corazziari, 2004).

The Mayo Clinic addresses the fact that although IBS is a chronic condition, the signs and symptoms associated with this disorder often fluctuate. The Mayo Clinic defines IBS is a multifactorial syndrome brought upon by a combination of both environmental and genetic determinants http://www.mayoclinic.com/health/paragard/MY00997, 2012). Current literature does not provide a model as to why many patients experience drastic fluctuations in their symptoms, and due to these fluctuations, providers have had a difficult time providing treatment to their patients. The model of progesterone, one of the hormones influencing stress throughout the body and an ovarian hormone much more pronounced in women than in men, as a key regulator of the symptoms

associated with IBS provides a novel mechanism behind the clear fluctuations in symptoms.

Treatments for IBS have not proven to be too beneficial. Because this syndrome is not understood on the pathologic level, the therapies prescribed are usually targeted to relieve individual symptoms (Camilleri et al., 2009). It is important to attempt to develop therapies that target the underlying mechanisms of painful IBS rather than just targeting the symptoms (Trinkley et al., 2010) so that we can create novel therapies that are causally directed, improving gastrointestinal function and health (Anderson et al., 2011).

It is important to look at this syndrome from an epidemiologic perspective. The prevalence of women who suffer from this syndrome as compared to men is much more pronounced (Makhari, 2011). In fact, women are twice as likely to suffer from IBS than men (Chang et al., 2006). Not only do women suffer more from IBS than men, but women with IBS are more likely to report dysmenorrhea and premenstrual distress syndrome as compared to women who do not suffer from IBS (Heitkemper et al., 2006). This may suggest that there is a connection between the pain experienced during IBS and the hormones that surge throughout the menstrual cycle. Although the gender related differences seen in IBS are likely multifactorial involving environmental, psychological, genetic and biological factors, the event of gonadal maturation coinciding with the onset of painful IBS symptoms suggests that these two events are not independent (Heitkemper et al., 2008).

Gastrointestinal transit time has been found to be markedly slowed during the luteal phase of the menstrual cycle, when the hormone progesterone is dramatically elevated, as compared to the follicular phase in women suffering from IBS, suggesting that the hormone progesterone has a profound effect on the gastrointestinal symptoms associated with IBS (Heitkemper et al., 2001). Progesterone is also markedly increased during the second and third trimesters of pregnancy, and these elevated levels during pregnancy are congruent with the exacerbated gastrointestinal symptoms, such as constipation and cramping, that often occur in IBS patient throughout the course of their pregnancy (Druckmann et al., 2005).

Constipation, a very serious and clinical problem associated with slow colonic transit, affects close to 20% of the US population and is seen primarily within the female population (Gonenne at al., 2006). These symptoms often begin during at menarche, when women experience their first menstrual period, and are relieved once menstruation begins when levels of progesterone and estradiol levels dramatically drop resulting in looser stools (Gonenne at al., 2006). While an increase in IBS-like symptoms has been shown to occur during the luteal phase of the menstrual cycle and during pregnancy when progesterone levels are high, a decline in IBS-like symptoms has been indicated following menopause, when the ovaries' production of estrogen and progesterone decrease dramatically (Palsson et al., 2013), further suggesting progesterone's role in modulating the gastrointestinal symptom fluctuations found in patients suffering from IBS.

This thesis takes a deeper look into the possible mechanisms behind progesterone's influence over the gastrointestinal symptoms by evaluating its relationship with secretin, gastrin, CCK, gastric inhibitory peptide, and motilin; the prominent hormones found throughout the gastrointestinal tract. One possible mechanism looks at progesterone's effects on G proteins and the hormone, vasoactive inhibitory peptide also known as VIP. It was concluded that an overexpression of progesterone receptors in conjunction with elevated levels of progesterone may cause an upregulation of G proteins, thereby increasing the hormone vasoactive inhibitory peptide (VIP), a prominent hormone responsible for inhibiting smooth muscle contractions (Cheng et al., 2010). This link may provide a possible mechanism for progesterone's role in inducing constipation and cramping (Gonenne et al., 2006).

High levels of progesterone were found to correspond to low levels of motilin, a hormone responsible for inducing gastrointestinal activity following a meal, suggesting that progesterone has a dominant and inhibitory effect over the gastrointestinal hormone motilin (Qiu, 1993). Inhibiting motilin, a hormone that along with CCK initiates gut contractions, could cause the severe constipation and cramping associated with IBS.

Progesterone has also been suggested as a possible gastrin inhibitor, and patients from this study with low levels of gastrin were found to have markedly increased symptoms of constipation, further elaborating on progesterone's role as an inducer, causing fluctuations in the various gut hormones; hormones that could

very well be causing many of the symptoms associated with painful IBS (Preston et al., 1985).

Studies that looked a the correlation between progesterone and some of the gut hormones such as VIP, motilin and gastrin provide possible mechanisms underlying progesterone's dominant role in modulating and inducing many of the symptoms associated with IBS. Many of the fluctuations associated with patients' symptoms correspond to the fluctuations in progesterone levels seen during the menstrual cycle, throughout pregnancy and post-menopause when the levels are dramatically reduced. Looking at progesterone and its effects on the intestinal hormones and symptom fluctuations will allow providers to provide better and more directed therapies for patients suffering from IBS.

Future Research for Effective Therapies

In order to provide relief for these patients, much more research is needed in order to understand the underlying mechanisms associated with these symptoms. Treatments should be targeted towards the mechanisms associated with causing these symptoms rather than targeted to the symptoms themselves at a very superficial level. Looking at progesterone as a possible hormone that potentially induces and/or exacerbates many of the symptoms associated with IBS and IBD could provide a novel approach to target therapeutic agents.

A possible course of treatment to provide relief that is also targeted towards a potential mechanism could be to place women suffering from severe IBS-like symptoms on hormone replacement therapy such as estrogen and progesterone or just progesterone. This way, the spikes in progesterone that may induce constipation and cramping would be eliminated, providing much sought after relief for the patient. Therapies should be researched that act as progesterone receptor antagonists localized in the gut. This kind of therapy would also alleviate many of the symptoms associated with increased levels of progesterone or progesterone receptors throughout the intestinal tract.

Irritable Bowel Syndrome and Inflammatory Bowel Disease remain as two of the most mysterious and convoluted diseases. It is important to look into the mechanisms behind the problems associated with these diseases in order to better treat the hundreds of thousands of individuals that suffer every day from these conditions. Progesterone as well as other hormones, and their interactions with the gut should be further evaluated in order to continue to better understand these conditions and help those suffering.

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