Overlapping Conditions in Women With Irritable Bowel Syndrome

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Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders diagnosed in the United States. IBS is characterized by abdominal pain and alterations in bowel patterns (such as diarrhea, constipation). It is estimated that 10% to 17% of the general population are affected by varying degrees of symptoms. These symptoms account for absences from school, missed work, reduced productivity, diminished quality of life, as well as tremendous costs associated with treating this disorder.

In 2000, the direct and indirect costs of diagnosis and symptom management of IBS were estimated to be $1.66 billion, making it not only costly to the individual but also to the health care system (Levy et al., 2001; Sandler et al., 2002). Leong and colleagues (2003) found that the total health care expenditures per year for the individual with IBS were $4,527 as compared to $3,276 for an age and gender-matched control in 1998. Excess surgeries are among the undesirable health care events related to an IBS diagnosis (Feld et al., 2003). In addition to health care utilization, the impact of IBS has been measured in the poorer quality of life of patients as well as missed work/school and reduced productivity (Motzer, Hertig, Jarrett, & Heitkemper, 2003; Whitehead, Burnett, Cook, & Taub, 1996).

In most countries, including the United States, the prevalence of IBS is approximately 2 to 2.5 times greater in women than men (Camilleri & Choi, 1997). This imbalance has prompted clinicians and investigators to examine factors that account for gender differences in IBS (for review see Chang & Heitkemper, 2002). Such studies have demonstrated that women with IBS are more likely to report a history of constipation whereas men are more likely to report diarrhea. In addition, women with IBS are more likely than men to report extraintestinal disorders including migraine headaches, bladder discomfort, dyspareunia, and chronic pelvic pain (Lee, Mayer, Schmuelson, Chang, & Naliboff, 2001). The focus of this article is to explore current thinking related to the etiology and pathophysiology of IBS along with its relation to other pelvic organ conditions especially chronic pelvic pain (CPP) and interstitial cystitis (IC). Finally, diagnosis and management of IBS will be discussed.

Etiology and Pathophysiology

IBS is a heterogeneous condition as exemplified by the differences in predominant symptoms (for example, constipation, diarrhea, alternating stool pattern), symptom frequency (for example, daily vs. weekly), and symptom severity (mild to very severe). The heterogeneity of IBS has made it challenging to define a single, unifying hypothesis related to its cause.

It has been suggested that IBS may be a three-component disorder characterized by dysfunctions in GI motor activity, visceral sensation, and/or the processing of information by the central nervous system (CNS) (Camilleri & Spiller, 2002). Symptoms of IBS (constipation, bloating, and diarrhea) suggest altered gut motility; existing data support the theory of altered motility in the pathogenesis of IBS. In a recent report,
The notion that CNS dysfunction may be present in IBS is supported by studies using both PET and functional MRI. The perception of acute rectal stimulation is associated with anterior cingulate cortex activation in controls while patients with IBS showed an aberrant brain activation pattern both during noxious rectal stimulation and in anticipation of rectal pain (Silverman et al., 1997). Gender-related differences in brain activation patterns in response to colonic distention have also been noted (Naliboff et al., 2003).

Overlap with Other Conditions

As stated previously, extra-GI conditions associated with IBS are numerous. In a review of the published literature on IBS since 1966, Whitehead, Palsson, and Jones (2002) noted that non-GI, nonpsychiatric disorders with the best-documented association with IBS included fibromyalgia (49% have IBS), chronic fatigue syndrome (51%), temporomandibular joint disorder (64%), and chronic pelvic pain (50%). Similar to IBS, the female predominance in these conditions is well documented. Of these, the overlap in CPP and IC with IBS in women will be addressed.

The overlap of gynecologic conditions and IBS was noted by Prior in an early study in which patients waiting in a gynecologist’s office were surveyed regarding their symptoms (Prior, Wilson, Whorwell, & Faragher, 1989). They noted that approximately 50% of the women had symptoms compatible with a diagnosis of IBS. CPP is a chronic condition, defined as pelvic pain of at least 6 months duration, and is estimated to affect approximately 15% of women (Gelbaya & El-Halwagy, 2001; Gunter, 2003). As such, CPP covers a wide range of reproductive disorders including dysmenorrhea, endometriosis, and pelvic congestion as well as bowel (IBS) and urinary tract problems (such as IC). In addition, the muscle wall and the nerves innervating abdominal organs may contribute to CPP. As with IBS, CPP may be related, at least in part, to visceral hypersensitivity and is thought to involve multiple systems including the neurologic, musculoskeletal, and endocrine systems. Gelbaya and El-Halwagy (2001) have suggested that the co-morbidity of IBS and CPP may range from 65% to 79%; others have noted a somewhat lesser overlap. Walker, Gelfand, Gelfand, Green, & Katon (1996) found a 35% prevalence of CPP in women with IBS compared to 14% in those with inflammatory bowel disease. Walker also noted similarities in psychiatric profiles between women with IBS and CPP. In addition, those with both IBS and CPP had a higher lifetime history of dysthymic and panic disorders as compared to those with IBS alone (Walker et al., 1996).

Of those who present for health care services with CPP, 5% to 10% have IC (Reiter, 1998). IC is a painful, sterile, disorder of the urinary bladder that is characterized by urgency, frequency, nocturia, and pain. Similar to IBS and CPP, IC disproportionately affects women. Giambardino (2000) pointed out that the symptom description of IC (urgency, frequency, and bladder pain generally relieved by voiding) is parallel to the description of IBS-diarrhea predominant (urgency, frequency, and abdominal pain relieved by defecation). In a survey of 2,405 patients with IC, IBS was the second most commonly associated medical condition after allergies (Giambardino, 2000). It has been suggested that the overlap between IBS and other abdominal organ conditions such as IC and CPP may be related to activation of peripheral visceral afferent fibers. Given the researchers found that 100 IBS subjects with alternating constipation and diarrhea had delayed gastric emptying and oral-cecal transit time as measured by ultrasonography and hydrogen breath analyses, respectively (Portincasa, Moschetta, Baldassarre, Altomare, & Palasciano, 2003). However, methodologic issues make it challenging to study motility and symptom experiences in IBS and there is often a lack of a direct correlation between motility characteristics and actual symptoms reported by patients (Clemens, Samsom, Roelofs, van Berge Henegouwen, & Smout, 2003).

Numerous studies provide data to implicate heightened visceral sensitivity in IBS (Berman et al., 2002; Hu & Talley, 1996). A number of investigators have shown that stimulation of GI visceral afferents via balloon distention (such as barostat) results in differential responses in IBS versus non-IBS individuals. Patients with IBS tend to report increased discomfort with balloon distention at lower volumes than individuals without IBS. This “visceral hyperalgesia” may explain the role of specific dietary substances in IBS symptoms. For example, sorbitol, fructose, and lactose intolerance are associated with increased gas production and may subsequently trigger abdominal discomfort secondary to bowel lumen distention. It is well documented that patients with IBS report a greater number of symptoms compatible with a history of psychopathologic disorders, abnormal personality traits, psychological distress, and sexual abuse (Koloski, Talley, & Boyce, 2001; Weinryb et al., 2003). Moreover, levels of daily psychological distress are positively associated with GI symptoms in women with IBS (Jarrett et al., 1998). The co-morbidity of mood disorders with IBS may also contribute to visceral pain or discomfort perception at the level of the CNS.
overlap in afferent neural pathways from the urinary, reproductive organs, and GI tract at both the spinal and supraspinal levels, it is logical to envision the co-existence of conditions affecting these hollow organs.

Symptom reports in IBS, CPP, and IC tend to be episodic and chronic. Women with IBS, IC, and CPP also report higher levels of dyspareunia relative to those without these conditions (Fass, Fullerton, Naliboff, Hirsh, & Mayer, 1998; Reiter, 1998). In all three conditions, symptoms are often triggered or amplified by menstrual cycle phase. Heitkemper et al. (2003) reported that women with IBS experience an amplification of symptoms such as abdominal pain, bloating, and diarrhea immediately premenstrual and the first 2 days of menstrual flow. In women with IBS, the colonic visceral threshold was significantly lower at menses than during the other four cycle phases (Houghton, Lea, Jackson, & Whorwell, 2002). This has led investigators to suggest that circulating estrogens may play a role. Estrogens can act via a number of mechanisms including direct effects on bowel or urinary bladder walls. Bennett, Gustafsson, and Keast (2003), using an animal model, noted that estrogen can have a direct action on gene expression in the bladder primary afferent neurons, to alter their excitability and intracellular signaling. Thus, estrogen may also modulate afferent fiber activation, spinal cord sensory transmission, and CNS processing of sensory input. It is clear that additional research is needed to assess the relationship of these conditions more closely with respect to etiology, symptom triggers, and physiological consequences. At the same time greater awareness of these overlapping conditions challenges clinicians in terms of diagnosis and successful management in patients with co-existence of these conditions.

**Diagnosis of IBS**

Diagnosis of IBS begins with a careful history, review of systems and symptom assessment. The diagnosis of IBS is based on positive symptoms and exclusion of pathology. There is no definite objective (such as blood test, x-ray) indicator for IBS. Since 1978, the diagnostic criteria for IBS have been evolving. The Manning criteria were the first, followed by the Rome I criteria in 1989 and then the Rome II criteria for IBS in 1999 (Drossman, Talley, Whitehead, Thompson, & Corazziari, 1999). These latter two sets of criteria were developed by a multinational group of clinicians and researchers to establish criteria to be used in clinical trials research. As shown in Table 1, the Rome II criteria are based on the presence of abdominal pain along with changes in bowel pattern, such as diarrhea or constipation. Recent nationally published guidelines have recommended the use of symptom-based criteria in clinical practice (American College of Gastroenterology, 2002). The criteria are used concomitantly with a review for “red flags” (see below). A 2002 systematic review of the literature indicated that increased diagnostic testing did not result in an increase in the diagnosis of functional GI disorders (Cash, Schoenfeld, & Chey, 2002).

**Table 1. The Rome II Criteria for Irritable Bowel Syndrome**

<table>
<thead>
<tr>
<th>Abdominal discomfort or pain for at least 12 weeks (need not be consecutive) within 12 months that has at least two out of three features:</th>
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<tr>
<td>• Relieved with defecation.</td>
</tr>
<tr>
<td>• Onset associated with a change in frequency of stool.</td>
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<tr>
<td>• Onset associated with a change in form (appearance) of stool.</td>
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Source: Thompson et al., 1999

**Management**

Since treatment of IBS is often focused on specific symptoms, patients are encouraged to maintain a 1 to 2 week symptom diary or log. This also has the benefit of allowing the patient to note when and what symptoms
occur and potentially identify triggering events. Such diary keeping is often helpful for patients in terms of making connections between stress, diet and, for women, menstrual cycle phase and symptoms. For patients in whom there is a question of lactose intolerance, a 1 week trial of excluding dietary lactose (milk products) may help alleviate symptoms. Similarly patients who can reduce sorbitol, fructose, and gas-forming foods may experience a reduction in symptoms. However, adherence to a strict exclusionary diet is difficult for most individuals.

Nondrug therapies play an important role in IBS management. Behavioral therapies are focused on reducing stress and stress-related triggers of IBS symptoms, increasing relaxation, and reducing negative self-talk. Examples of behavioral therapy include relaxation therapy, biofeedback, hypnotherapy, cognitive therapy, and psychotherapy. In a recent multi-site study, Drossman and colleagues (2003) found that women with IBS showed an improvement in global satisfaction and quality of life following cognitive behavioral therapy as compared to education alone. Our research team has recently demonstrated the efficacy of an 8-week cognitive behavioral therapy delivered by an advanced practice nurse in reducing GI symptoms and enhancing quality of life in women with IBS (Heitkemper et al., in press).

Historically, drug treatment for IBS focused on specific symptoms (such as abdominal pain, diarrhea, constipation) (see Table 2). Many of these drugs have been used in spite of little to no randomized clinical trial data.

Antispasmodic agents (for example, dicyclomine, hyoscyamine) work through anticholinergic mechanisms to reduce abdominal pain. At high doses these drugs can produce other anticholinergic side effects, which limit their use in some patients, especially those with constipation.

Bulking agents (such as wheat bran, psyllium, calcium polycarbophil, ispaghula, and corn fiber) are commonly used to reduce constipation. Since patients have reduced intestinal transit, bulking agents are used to accelerate transit. Patients should be informed that increasing dietary fiber could result in an initial increase in bloating and abdominal discomfort that tends to decrease over time.

Patients with diarrhea-predominant IBS have accelerated intestinal transit and may get symptomatic relief from antidiarrheals such as loperamide that reduce transit time. Antidiarrheal drugs are used intermittently for diarrhea management but have little effect on abdominal pain.

Antidepressants represent another category of drugs that are used in IBS management. These agents are thought to work via a reduction in visceral hypersensitivity at the level of the visceral afferent fibers. Tricyclic antidepressants (TCAs: desipramine, amitriptyline) have been used at doses lower than that used for depression treatment for their efficacy in chronic pain management. However, TCAs should be used cautiously in patients with constipation because of their

<table>
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<tr>
<th>Agent</th>
<th>Symptom Relief</th>
<th>Side Effects</th>
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<tr>
<td>Bulking agents (such as psyllium) Laxatives</td>
<td>Constipation</td>
<td>May produce gas initially. Regular use may result in fluid and electrolyte problems.</td>
</tr>
<tr>
<td>Antidiarrheals (such as loperamide)</td>
<td>Diarrhea</td>
<td>Used on a per need basis; not intended for regular use.</td>
</tr>
<tr>
<td>Antispasmodies (such as dicyclomine, hyoscyamine)</td>
<td>Abdominal pain</td>
<td>Anticholinergic properties may contribute to constipation.</td>
</tr>
<tr>
<td>Antidepressants (such as tricyclic antidepressants, desipramine)</td>
<td>Abdominal pain</td>
<td>Anticholinergic properties may contribute to constipation.</td>
</tr>
<tr>
<td>Serotonin (5-HT3) receptor antagonist (such as alosetron*)</td>
<td>Abdominal pain and diarrhea</td>
<td>Constipation</td>
</tr>
<tr>
<td>Serotonin (5-HT4) receptor partial agonist (such as tegaserod)</td>
<td>Constipation</td>
<td>Diarrhea</td>
</tr>
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</table>

* FDA approved for women with severe diarrhea only; reserved for patients who have failed to respond to other IBS treatments. Patients receiving this drug must be educated about potential complications and followed medically.
anticholinergic properties. The efficacy of selective serotonin reuptake inhibitors are less well studied in patients with IBS. Initial GI side effects of these drugs may influence patient compliance. Due to increased prevalence of depression in patients with IBS, antidepressants at higher doses may be beneficial because of their mood effects.

Newer drugs used in IBS management include agents that work on serotonin (5-HT) receptors. The GI tract contains approximately 90% to 95% of the body’s 5-HT; much of which is located in the enterochromaffin cells lining the bowel wall. Serotonin acts through a variety of different receptor subtypes in the gut including 5-HT3 and 5-HT4. Serotonin release in the bowel subsequent to bowel distention has been associated with changes in motility, secretion, and possibly pain transmission. Alosetron, a 5-HT3 receptor antagonist, was approved by the FDA for treating diarrhea and abdominal pain in women with IBS. This agent was removed from the market in 2000 because of concerns related to ischemic colitis and severe constipation. In 2002, the drug was returned to the market with restricted marketing of the drug for women with severe IBS who have failed other therapies. More recently tegaserod, a 5-HT4 partial agonist, was approved by the FDA for managing women with constipation-predominant IBS. The efficacy of these drugs in reducing symptoms in patients with alternating bowel patterns as well as men remain to be explored further.

Less is known about the use of complementary and alternative therapies for IBS. Peppermint oil and caraway oil are frequently used as herbal remedies for abdominal discomfort and pain. Both reduce small intestine transit (Goerg & Spilker, 2003); however, randomized clinical trials to test their efficacy in IBS management are lacking. Recent evidence suggests that a protocol of multiple sessions of hypnosis is also effective in reducing abdominal pain in patients with IBS (Gonsalkorale, Miller, Afzal, & Whorwell, 2003). However, the long-term benefit of such therapies remains to be determined.

A comprehensive treatment plan for women who have multiple concurrent conditions such as CPP, IBS, and IC has not been developed and tested. The lack of reliable data related to the effects of disorder-specific therapies on other conditions contributes to the problem. For example, what is the impact of anti-seizure medications used in IC on symptoms or bowel patterns associated with IBS? It is probable that treatments for IC that focus on modulating bladder sensory nerve stimulation (neurolytic agents) or inhibit neurogenic activation of mast cells may also have some value in reducing GI symptoms associated with IBS. At the same time, it is known that the use of anticholinergic medications for bladder symptoms may aggravate the constipation in patients with IBS. Using antidepressants as well as analgesics for visceral pain modulation in patients with CPP could have both positive and negative consequences related to GI symptoms. Conversely, it is not known whether newer serotonergic agents used in IBS have an impact on symptoms related to IC and CPP. In IBS, IC, and CPP cognitive behavioral therapies have been used to reduce triggers and enhanced quality of life. More specifically stress reduction, relaxation training, and identifying and reducing negative thoughts are utilized. However, the impact of cognitive behavioral therapy in women with overlapping syndromes remains to be determined.

Summary

Despite ongoing research as to its etiology and pathophysiology, IBS remains a poorly understood condition. Greater attention is needed to focus on the co-morbidity of conditions in patients with IBS and their potential contributory to understanding and managing the disorder. Nurses, especially those who work with patients with urologic and gynecologic conditions, are in an ideal position because of their direct contact with patients to educate them about IBS, its triggers, and therapeutic options.

References


and treatment. Obstetrical and Gynecological Survey, 58(9), 615-623.


