Hormonal Influences on the Gastrointestinal Tract and Irritable Bowel Syndrome

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Irritable bowel syndrome (IBS) is a common disorder of gastrointestinal (GI) function that affects more women than men in most Western countries. Often among women, symptoms of IBS appear to be related to hormone status (e.g., menstruating, pregnant, menopausal, taking oral contraceptives or hormone replacement therapy). In some women, symptoms wax and wane in concert with their menstrual cycle. One potential explanation for the observed variability in IBS symptoms is that sex hormones affect GI motility and function. The purpose of this review is to describe the growing body of evidence that supports a role for sex hormones in the pathophysiology and/or symptom presentation of IBS.

IBS: CLINICAL SYMPTOMS

IBS is a disorder in which abdominal pain or discomfort is a primary symptom. It is accompanied by a change in bowel habit and abnormal stool frequency (defined as >3 bowel movements per day [diarrhea] or <3 bowel movements per week [constipation]) (1). IBS patients also commonly report hard or loose/watery stools, a feeling of incomplete evacuation after bowel movement, bloating and/or abdominal distension, and the passage of mucus.

IBS: EPIDEMIOLOGY

Reported prevalence rates range from 3% to 20%, with most estimates concentrated between 10% and 15% (2). Although IBS affects individuals of all races and both sexes, women are more commonly affected than men in Western nations at a ratio of approximately 2:1, a phenomenon that has yet to be completely explained (3–6). In North American studies, the female predominance is greater among individuals who seek medical attention (3–4:1) as compared with those who do not (<2:1) (7); however, it is unclear if this reflects under-reporting in men or a true predominance in women. Sex differences in presentation of symptoms have been described, including more IBS with diarrhea among men and more IBS with constipation and bloating among women (8). IBS is one of the most common disorders seen in the primary care setting. Women often present to their gynecologist first, as this may be...
the only physician they ever see. IBS accounts for 12% of diagnoses in the primary care setting (5) and is responsible for 30% to 50% of referrals to gastroenterologists (9).

Coexistence of IBS and Other GI Disorders
IBS often coexists with other GI disorders, both functional (e.g., dyspepsia, chronic constipation) and organic (e.g., celiac disease, gastroesophageal reflux disease, inflammatory bowel disease [IBD]) (10). Furthermore, many patients with IBD are diagnosed initially with IBS (11,12). However, once a diagnosis of IBD is established, comorbid IBS tends to be underdiagnosed and undertreated. Studies have shown that more than 40% to 57% of Crohn’s disease patients and one third of ulcerative colitis patients who were in remission had comorbid IBS (11,13). IBS can contribute to symptoms of IBD, especially in quiescent disease, if the symptoms of IBS are mistaken for an IBD flare. This results in IBD overtreatment and IBS undertreatment.

IBS: IMPACT
IBS symptoms affect the lives of patients and their families. Several studies have reported negative effects on quality of life (14–16), as well as on work-related and social activities (17–20). The direct costs associated with IBS are estimated to be as high as $10 billion per year, and indirect costs as high as $20 billion annually (excluding prescription and over-the-counter drug costs) (21,22).

IBS: A ROLE FOR HORMONES?
A variety of observations support the hypothesis that female sex hormones, and fluctuations thereof, may have an impact on IBS, including the simple fact that more women than men experience IBS. Men with IBS have lower serum luteinizing hormone (LH) than men without IBS, suggesting a potential protective effect of this hormone (23).

Additional evidence comes from reports of menstrual cycle-related symptom fluctuations. Many women with IBS report that symptoms fluctuate with their menstrual cycles and that flares occur in the perimenstrual and perimenopausal phases (24–26). Alterations in rectal sensitivity (27) (increased during menses) and GI transit, which is increased during the follicular phase compared with the luteal phase (28,29), also have been reported. Other studies showed that menses (a time of declining/minimal ovarian hormone levels) was associated with looser stools compared with the follicular and luteal phases (30,31). Furthermore, IBS is diagnosed more often in women with dysmenorrhea than in those who cycle normally (32).

Changes in hormone status associated with pregnancy or menopause also may influence symptoms. During pregnancy, a time during which estrogen and progesterone levels are high, GI symptoms increase and intestinal transit decreases (28). Reports of abdominal bloating increase after menopause, primarily among women who are not receiving hormone replacement therapy (HRT) (34).

These thoughts are all intriguing, but exactly how hormonal factors influence IBS remains unclear. There also exists the question as to whether hormone differences are associated with specific symptoms (e.g., bloating) or with the wider spectrum of IBS symptoms.

Cycling Female Sex Hormones
During the reproductive years in women, the normal menstrual cycle is characterized by predictable and cyclic changes in estrogen and progesterone levels (Figure 1) that may influence bowel activity. In the follicular phase, or immediate postmenstrual phase, estrogen predominates and progesterone levels are low. Responding to follicle-stimulating hormone (FSH) secretion from the pituitary gland, the granulose cells of the ovarian follicles secrete gradually increasing levels of estradiol, which peak around day 13, inducing the pituitary LH surge that heralds ovulation. The intra-ovarian events leading to ovulation involve estrogen-induced production of prostaglandins, primarily prostaglandin F2α (PGF2α), PGE2, and prostacyclin, all of which are measurable in follicular fluid. The
release of this prostaglandin-rich fluid is thought to cause the pain that sometimes occurs with ovulation.

After ovulation, the corpus luteum secretes both estrogen and progesterone. Progesterone levels peak 8 to 9 days after ovulation. Rising luteal phase estrogen levels are thought to induce luteolysis, mediated by PGF2α via endothelin-1 and tumor necrosis factor-alpha (TNF-α) in the corpus luteum. With the decline of the corpus luteum, estrogen and progesterone levels drop, triggering the events in the uterine endometrium that lead to menstruation. These events involve complex interplay of prostaglandins, cytokines, and other lytic enzymes.

The endometrium also produces prostaglandins, the predominant one being PGF2α, with lower levels of PGE2 also produced. PGF2α release leads to smooth muscle contraction, ischemia, and sensitization of nerve endings; PGE2 is a smooth muscle relaxant. Other molecules produced include endothelin-1, metalloproteinases, TNF-α, and cytokines. Endometrial prostaglandin levels are three times higher in the luteal than in the follicular phase. Levels are highest

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during menstruation, when most PGF2α release from the endometrium occurs. Women who experience dysmenorrhea have greater endometrial prostaglandin levels than do asymptomatic women, and they have higher levels of PGF2α in their menstrual fluid (35). Prostaglandin production has been thought to influence diarrhea associated with menses by inhibiting transepithelial ion transport in the small intestine.

The perimenopausal transition is characterized by its unpredictability and by wide fluctuations in estrogen levels throughout the cycle. Levels of estradiol may be markedly increased because of ovarian follicular response to elevated FSH levels. There may be a relative progesterone deficiency due to lack of ovulation or luteal phase deficiencies as the quality of the ovarian follicles diminish. This estrogen-dominant environment can occur even in the presence of hot flushes, and leads to irritability, breast tenderness, and bloating. Bloating can occur when estrogen induces nitric oxide synthetase, which relaxes the smooth muscle in the gut. This nitrogen oxide synthetase induced smooth muscle relaxation clinically results in bloating.

**Potential Hormonal Influences on the GI Tract**

Estrogen, TNF-α, endothelin, and prostaglandins also exert effects on the GI tract. Estrogen receptors are found throughout the GI tract (36) in components of the pelvic floor (37) and in sensory neurons of the dorsal root ganglia (38), suggesting that female sex hormones may play a role in IBS symptomatology. Studies have shown that estrogen and progesterone exert many effects on the GI tract (36). These hormones have a relaxing effect on the lower esophageal sphincter and decrease colonic transit. TNF-α induces inflammation, delays gastric emptying, increases colonic transit time, and induces flow of fluid into GI tissues. Endothelin has potent effects on GI smooth muscle, leading to contraction of the esophagus, stomach, and intestines, and has a modulatory effect on GI motility (39). It also is a potent stimulator of gallbladder motility, stimulates sphincter of Oddi motility, and decreases trans-sphinicteric flow (39).

Prostaglandins are a diverse set of molecules derived from the modification of essential fatty acids. When present at the proper time, place, and amount, these local chemical messengers play a vital role in numerous functions, maintaining homeostasis. In the gut, prostaglandins, particularly those of the E type, are implicated in the proper maintenance of mucosal blood flow, stimulation of the mucous secretion lining the gut surface, stimulation of GI motility, and secretion of bicarbonate to help neutralize acids (40). Altered prostaglandin levels can result in abdominal pain, colonic contractions, and diarrhea.

In women who experience dysmenorrhea, there is a significant increase in the uterine expression of PGF2α (41), which is the likely explanation for the increased pain associated with their menstruation. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common treatment modality; however, use of these agents can lead to GI depletion of prostaglandins (42). Medications to reduce acid production, neutralize the acid, or coat the lining of the GI tract often are used as adjunctive therapies in patients taking NSAIDs for chronic conditions. Misoprostol (Cytotec®) is a synthetic PGE1 analog that stimulates secretion of gastric mucus and production of bicarbonate; prostaglandins provide a protective effect for patients taking medications that inhibit GI COX enzymes. However, misoprostol also invokes prostaglandin effects in the uterus (uterine muscle contractions) that can lead to complications in pregnancy, including premature labor and abortion (Pfizer, data on file). Therefore, misoprostol should not be used in women known or thought to be pregnant. Alternatively, medications that inhibit production of gastric acid or coat the lining of the GI tract can provide protection to patients on long-term NSAID therapy.

**Clinical Evidence Linking Female Hormones to Bowel Function**

It has been postulated that cycling female sex hormones are related to changes in bowel habits. In the 1980s, alterations in GI transit (increased during the follicular phase compared with the luteal phase) (28,29) were reported. Heitkemper and colleagues (1988) reported that menses (a time of declining/minimal ovarian hormone levels) was associated with looser stools compared with the follicular and luteal phases (30). In contrast, high levels of estradiol and progesterone during
the luteal phase were reported to be associated with delayed GI transit (28), which may account for firmer stools during this phase of the menstrual cycle. Healthy women describe changes in bowel habits during their menstrual cycle, and women with IBD experience an even higher prevalence of GI symptom–related fluctuations. A suggestive physiologic mechanism may be the increased intestinal prostaglandin production that causes contraction of colonic smooth muscle or the increased intestinal secretions related to variation in progesterone levels (43).

Whereas other early clinical studies failed to show a relationship between female hormones and bowel function, a growing body of evidence suggests that such a relationship exists. Kamm and colleagues (1989) reported that, under normal physiologic conditions, sex hormones have no major effect on bowel function (44). They based this conclusion on their observation that mean transit times (whole gut transit) and stool weights were not significantly different during the follicular versus the luteal phase of the menstrual cycle in 18 healthy women. Furthermore, self-reported bowel frequency and stool consistency were not significantly different during the menstrual, follicular, or luteal phase.

However, Wald and colleagues (1981) described different findings in a more recent report of their study of hormone levels and GI transit times in 15 normally menstruating women (28). They measured serum estradiol and progesterone levels and GI transit times at 2 points during the menstrual cycle, once in the follicular phase (days 8–10) when progesterone levels are low, and once in the luteal phase (days 18–20) when progesterone levels are elevated. GI transit was determined via monitoring of breath hydrogen levels at 10-minute intervals after the ingestion of lactulose (to determine time from ingestion until delivery to the cecum). The authors reported that progesterone levels did increase during the luteal phase, as expected, and that GI transit time was significantly (P < 0.01) prolonged during this phase as compared with the follicular phase. Based on these findings, they concluded that the menstrual cycle plays a role in determining GI transit time in normally menstruating women.

Jackson and colleagues (1994) reported that, although the phase of the menstrual cycle may affect transit, it did not appear to affect rectal motility or sensitivity in 20 healthy women (31). However, in their later study of 29 female patients with IBS, they found that, in contrast to healthy women, women with IBS had increasing levels of rectal sensitivity at the time of menses compared with all other phases of the menstrual cycle (27). This increase in rectal sensitivity was not related to changes in rectal compliance or wall tension. The authors considered the possibility that, because acute episodes of diarrhea are associated with increases in rectal sensitivity in women (but not men) and IBS patients are more susceptible to sensitizing events, this may be an explanation for the increased rectal sensitivity noted in IBS patients at menses. The authors also posed a second explanation—that prostaglandin release during menses may play a role in rectal sensitivity. Because the GI system of IBS patients may already be sensitive, the release of prostaglandins, known to induce afferent nerve sensitization, may be enough to trigger a further increase in this sensitivity. The authors also noted that anxiety and depression remained unaltered throughout the menstrual cycle—a finding that was consistent with past studies demonstrating that psychological traits are not associated with perimenstrual bowel-related symptoms (25,45). Similar to past studies, Houghton, et al (2002) reported a significant worsening of abdominal pain and bloating and more frequent bowel movements during menses (27). They also reported firmer consistency of the stool during the luteal phase. Houghton and colleagues concluded that women with IBS are predisposed to fluctuations in visceral sensitivity associated with the menstrual cycle.

Further evidence for a role of female hormones in bowel function comes from studies conducted in women in the perimenopausal and postmenopausal states. Triadafilopoulos and colleagues (1998) prospectively studied 228 women (170 postmenopausal and 58 premenopausal) who presented for evaluation at a primary care practice facility; investigators used a previously validated GI symptom questionnaire designed to evaluate symptoms consistent with IBS (46). (At the time of their participation in the study, none of these women presented for evaluation of abdominal or genitourinary symptoms.) The authors (continued on page 70)
found that 38% of postmenopausal women reported altered bowel function, as opposed to 14% of premenopausal women (P < 0.001). However, the two groups did not differ in occurrence of abdominal pain, diarrhea, and constipation, which are symptoms suggestive of IBS. The prevalence of IBS-type complaints peaked at a high of 36% among the 40- to 49-year-old age group. Laxative usage, gaseousness/excessive flatulence, and heartburn/acid regurgitation were also more common among postmenopausal women than premenopausal women, with prevalence rates of 9.4% vs 3.4%, 48% vs 27%, and 34% vs 18%, respectively. Interestingly, estrogen use did not affect GI symptoms in either group. The authors concluded that there is a high prevalence of altered bowel function and IBS-like GI complaints among women in the perimenopausal and postmenopausal periods.

Copas and colleagues (2001) attempted to explain various pelvic floor disorders, including fecal incontinence, by evaluating hormone receptor expression in the levator ani muscle and fascia, which make up the pelvic floor (37). The study looked at 55 women undergoing surgery for asymptomatic gynecological (n = 10) or symptomatic urogynecological (n = 45) conditions. Twenty-four of the women, all of whom were symptomatic, were receiving HRT. Estrogen receptor (ER) expression in the levator ani fascia was increased significantly (P < 0.03) in symptomatic women not receiving HRT when compared with asymptomatic, age-matched women, but was significantly lower (P < 0.001) in symptomatic women receiving long-term HRT when compared with age-matched women without HRT. The authors concluded that ER expression is significantly higher in symptomatic women when compared with asymptomatic women of the same age, but that long-term use of estrogen leads to a significant decrease in ER expression. This may explain why long-term HRT does not appear to favorably impact pelvic floor disorders and suggests that down-regulation of receptors or relative tissue dominance of the progestin component of therapy is the cause.

Crowell and colleagues (1994) noted an overlap in diagnoses of dysmenorrhea and functional bowel disorders (FBDs) in their 12-month evaluation of 383 women (aged 20 to 40 years) who presented to a single Planned Parenthood clinic (32). Dysmenorrhea, as identified via history and physical examination, was present in 19.8% of patients. Functional bowel disorder, defined as abdominal pain with altered bowel function, was diagnosed in 61% of patients with dysmenorrhea compared with 20% of patients without dysmenorrhea (P < 0.05). A relationship between bowel symptoms (bowel symptom inventory [25]) and menstrual symptoms (Moos’ Menstrual Distress Questionnaire [47]) was evident throughout the study and was independent of psychological differences (i.e., neuroticism, as measured using the NEO Personality Inventory [48]). Prostaglandin levels were measured in vaginal dialysate on the first day of menses in a subset of subjects (n = 44) and were elevated in women with dysmenorrhea regardless of bowel symptoms. The authors concluded that the observed relationship between menstrual and bowel symptoms and the overlap in diagnoses of dysmenorrhea and functional bowel disease were evidence of a common physiologic basis for many of the symptoms characteristic of these disorders.

Data from an earlier study conducted by Heitkemper and colleagues (1992) also suggested a relationship between symptoms and the menstrual cycle in women with FBD. In this study, patterns of GI symptoms and select mood and somatic symptoms were evaluated across two menstrual cycles in a group of 19 women with and 39 women without FBD (45). Each day, women rated their GI, perimenstrual, and other symptoms and recorded stool frequency and consistency. Serum estrogen and progesterone concentrations were measured during menses and during the follicular and luteal phases. The group with FBD rated stomach pain, nausea, and diarrhea higher at menses than did the group without FBD. Stomach pain was higher during the remaining days as well. The group with FBD also reported higher levels of perimenstrual symptoms on six of the eight Menstrual Distress Questionnaire-T subscales (P < 0.01). Interestingly, the authors reported no significant group differences in ovarian hormone levels or stool consistency/frequency scores. This is in agreement with what is known about premenstrual syndrome—those who suffer from this condition do not exhibit differences in ovarian hormone levels compared with healthy individuals; rather, they differ in their

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responses to normal hormonal fluctuations, in this case, in the central nervous system and other target organs.

GI symptoms also appear to be influenced by the menstrual cycle in women with IBS. Whitehead, et al (1990) assessed differences in GI complaints between female patients at a family planning clinic and women with IBS or FBD who were referred to a gastroenterology clinic (25). (Criteria for diagnosis of IBS were abdominal pain plus altered bowel habits, but restrictive criteria for IBS were not satisfied.) All patients were asked whether gas, diarrhea, or constipation occurred during menstruation. One third of patients who denied symptoms of IBS or FBD reported that menstruation was associated with one or more bowel symptoms; however, patients with IBS were significantly more likely to experience exacerbations of each of these bowel symptoms, especially increased bowel gas. The authors noted also that reports of bowel symptoms during menstruation were not associated with psychological traits or with menses-related changes in mood.

Similarly, Heitkemper, et al (2003) reported in another study that women with IBS had higher symptom severity, in terms of somatic, psychological, and GI symptoms, than did women in a control group (49). Compared with controls, women with IBS had significantly more severe GI symptoms, including abdominal pain, gas, and bloating, and also reported a higher percentage of days with hard and with loose stools. GI symptoms were significantly affected by the menstrual cycle phase, with complaints worse during menses. Among women with IBS, oral contraceptive users reported fewer symptoms of abdominal pain than did nonusers; however, there were no significant differences between the two groups with respect to gas, bloating, constipation, and diarrhea. In a subsequent study of women with IBS, Heitkemper and colleagues (2004) described a specific relationship between bloating and menses-associated symptoms such as uterine cramping and breast tenderness (50).

In a study of 477 female patients with IBS, Lee, et al (2001) reported that 40% of all female patients with IBS reported menstrual cycle-related worsening of symptoms (8). Of women younger than age 45, 50.8% reported experiencing menstrual cycle-related worsening of symptoms. However, based on two findings, the authors argued against a significant role for menstrual cycle-related hormone fluctuations in causing symptom differences. First, when premenopausal women with IBS were compared with postmenopausal women, there was no significant difference in bowel habit predominance (i.e., constipation, diarrhea, or alternating constipation and diarrhea). Furthermore, when postmenopausal women were compared with a group of age-matched men, the same difference as in the total male and female samples was observed, highlighting the concept that menstrual status does not affect bowel habit predominance. The authors did report, however, that premenstrual women were two times more likely to complain of nausea than were postmenopausal women with IBS.

**Hormonal Influences on Serotonin Activity?**

Serotonin (5-hydroxytryptamine [5-HT]), which is produced mainly by and stored in enterochromaffin cells in the GI tract, is vital to normal gut function. It is responsible for initiating and maintaining peristalsis, mediating secretion in the GI tract, and modulating the sensation of pain (51,52). Recent research has uncovered a potential role for abnormal serotonin expression and/or signaling in IBS and other GI disorders (53). The potential effect of sex hormones such as estrogen and progesterone on serotonin remains to be elucidated. However, the importance of serotonin and its receptors, as well as serotonin polymorphisms, in predicting response to treatment is an area of interest. A recent study has shown that estrogen and progesterone influence the level of 5-HT type 3 (5-HT₃) receptor mRNA (54). In ovariectomized rats, lower levels of PGE2 and progesterone resulted in significantly higher amounts of 5-HT₃ receptor mRNA. When ovariectomized animals were treated with estradiol and progesterone, 5-HT₃ receptor transcript levels returned to normal. Additional studies highlight the importance of the serotonin reuptake transporter in IBS as polymorphisms in this gene resulted in a differential response to alosetron, a 5-HT₃ receptor antagonist that is used to treat diarrhea-predominant IBS (55,56). Collectively, these results suggest that 5-HT₃ receptor activity, which is a target of pharmacologic intervention in patients with diarrhea-predominant IBS, also is regulated by female sex hormones.
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HORMONAL INFLUENCES ON THE GASTROINTESTINAL TRACT AND IBS

IBS SYMPTOMS IN PATIENTS USING ORAL CONTRACEPTIVES

Oral contraceptive use should be investigated among patients seeking relief from GI symptoms. Because estrogen excess can cause nausea, bloating, and cyclic weight gain, patients taking preparations high in estrogen may benefit from switching to low-estrogen formulations (i.e., those containing only 20 µg of estrogen such as Loestrin 1/20®️, Micrette®️️, or Alesse®️️). After switching to low-estrogen formulations, patients experience less bloating and less weight gain. Preparations with increased progestin content (e.g., Demulen 1/35®️️) also may be beneficial, especially in patients with functional nausea who are also thin. Drosiprenone, a C21 progestin derivative of spironolactone that has both progestational and mineralocorticoid effects, is the primary component of the recently introduced oral contraceptive Yasmin®️️. It produces mild diuresis (similar to spironolactone 25 mg). Recipients typically lose weight initially (3–4 pounds) but return to baseline weight after 6 months. Patients taking Yasmin®️️ should avoid potassium supplementation or other medications that affect potassium levels, such as chronic daily NSAIDs or angiotensin-converting enzyme inhibitors. The effects of various types of HRT on the GI tract are not yet understood. Whether “natural” progestins will offer any advantage is not known.

SUMMARY

There now exists a considerable body of evidence supporting a role for sex hormones in the development of IBS symptoms. Sex differences in prevalence and symptom presentation, as well as differences and fluctuations based on hormone status, have been described. An important next step is to determine whether sex or hormone status affects the efficacy of standard management approaches. To this end, categorization and selection of patients for clinical trial participation should not focus solely on IBS subtypes, as they currently do (i.e., constipation, diarrhea, and alternators); they should also focus on sex and hormone status. Furthermore, the role of sex hormones (e.g., oral contraceptives, HRT) in the management of patients with IBS symptoms remains to be defined.

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