HHS Public Access

Author manuscript

Neurogastroenterol Motil. Author manuscript; available in PMC 2021 July 01.

Published in final edited form as:

Neurogastroenterol Motil. 2020 July ; 32(7): e13802. doi:10.1111/nmo.13802.

Sex as a Biological Variable in Irritable Bowel Syndrome

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Abstract

Background: The pathophysiology and mechanisms of irritable bowel syndrome (IBS) involve both central and peripheral mechanisms that result in altered perception, as well as changes in bowel functions. These dysfunctions are associated with motor, sensory, immune, barrier, and intraluminal perturbations, including the microbiota, and their products and endogenous molecules with bioactive properties. There is evidence that these mechanisms are altered in both females and males. However, there is also increasing evidence that sex is a biological variable that impacts a number of aspects of the mechanisms, epidemiology, and manifestations of IBS.

Purpose: The objective of this article is to review the evidence of the differences among genders of the following factors in IBS: the brain-gut axis and sex hormones, epidemiology, diagnostic criteria and prognosis, pain perception, colonic transit, abdominal distension, overlap with urogynecological conditions, psychological issues, anorexia, fibromyalgia, serotonin, and responsiveness to treatment of IBS. It is important to consider the variations attributable to sex in order to enhance the management of patients with IBS and the research of mechanisms involved in IBS.

Keywords

serotonin; hormones; urogynecology; sensation

Introduction: Features of Irritable Bowel Syndrome Common in both Sexes

Irritable bowel syndrome (IBS) is generally regarded as a disorder of the brain-gut axis. The pathophysiology and mechanisms of IBS involve both central and peripheral mechanisms that result in altered perception, as well as changes in bowel functions associated with motor, sensory, immune, barrier, and intraluminal perturbations, including the microbiota, and their products and endogenous molecules with bioactive properties. Studies of the global prevalence of IBS generally show a higher prevalence in females than males, although there are cultural differences noted in certain countries where male patients tend to present for

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Author's Contributions:

M. Camilleri: Conceptualization and authorship

Competing Interests: Michael Camilleri has received research funding from Allergan, Novartis, and Takeda, BirdRock Bio for single center research projects in the fields of irritable bowel syndrome and gastroparesis. He serves as an advisor to Allergan, Takeda and Ironwood, with compensation to his employer, Mayo Clinic, not to himself personally.

care more frequently than females,[1, 2] as occurs in countries such as India and Sri Lanka. The median incidence of physician-diagnosed IBS in 19 general population cohorts was 38.5 (IQR 20, 45.3) per 10,000 person-years, and risk factors identified in a review of 38 papers that studied risk factors for IBS were prior gastroenteritis, female sex, age (both young and old), anxiety and depression, life events/stress, frequent healthcare use, pain and sleep disorders.[3]

The cumulative effects of psychologic distress, visceral hypersensitivity, and abnormal colonic transit[4,5] are well established in the literature,[6] and the number of factors present in patients with IBS have recently been associated with patient-reported outcomes in IBS.[7]

Visceral pain is a significant mechanism in patients with diverse forms of functional disease or pain, and it has been proposed that there are loci of activation within the brain for different types of pain, including esophageal pain, miscellaneous visceral pain, and lower gastrointestinal pain resulting from distension, in healthy controls and in patients with IBS.[8]

There is also evidence that hypersensitivity of the rectum (evaluated by discomfort thresholds) in some patients with IBS is present in both males and females. However, rectal hypersensitivity is not observed in all patients with IBS, and can be as low as 21%.[6] Discomfort thresholds may normalize over time, while the IBS symptoms persist,[9] and colonic sensitivity in IBS is strongly influenced by a psychologic tendency to report pain and urge to defecate rather than increased neurosensory sensitivity.[10] While psychosensory modulation, stress, and hypervigilance are relevant to some patients with IBS,[11] they are not ubiquitous in patients with IBS, and further research has led to the demonstration that a variety of peripheral mechanisms that initiate perturbation of gastrointestinal motor and sensory functions can lead to IBS symptoms.[12]

There are also multiple organic dysfunctions that result in symptoms that overlap with those of IBS, as diagnosed by symptom-based criteria. These include chronic constipation associated with evacuation disorders,[13] most commonly due to spastic conditions affecting the pelvic floor or anal sphincters and, more rarely, descending perineum syndrome. These conditions result in constipation, straining, a sense of incomplete evacuation, bloating, and left-sided abdominal pain that is relieved by bowel movements, which overlap with symptoms classically associated with constipation-predominant IBS (IBS-C).

Other organic conditions may stimulate IBS with diarrhea (IBS-D), and these include sugar maldigestion, food allergy/intolerance (including gluten), celiac disease, bile acid diarrhea, mucosal immune activation stimulating lymphocytic or microscopic colitis, mast cell infiltration, small intestinal bacterial overgrowth,[12,14] and increased circulating serotonin levels, particularly in the postprandial period.[15,16]

The most consistent findings regarding the microbiome in IBS (compared to controls) are reductions in *Bifidobacterium* and *Fecalibacterium* and increases in *Lactobacillaceae, Bacteroides* and *Enterobacteriaceae*. However, there were no consistent differences in the gut microbiome among patients with IBS-D and IBS-C.[17]

Identification of the mechanisms of IBS in individual patients offers the option of targeted management such as with modulation of colonic transit, bile acid sequestration, serotonergic agonists or antagonists, or glutamine for alteration of the intestinal barrier function in post-infectious IBS.[18,19]

Given these diverse mechanisms involved in the development of IBS, it is relevant to understand whether there are differences in manifestations of IBS between females and males and to examine whether sex impacts mechanisms; this may potentially lead to improved management of patients.

IBS: Are There Sex and Gender Differences?

Epidemiology and gender

In Western countries, the female to male ratio of IBS is 2:1. In the U.S. Householder Survey of functional gastrointestinal disorders, 14.5% of women and 7.7% of men had IBS symptoms.[20] In addition, there is a predominance of women compared to men who seek healthcare services for IBS in the U.S.[21] In contrast, in Asian countries (e.g., India and Sri Lanka), the prevalence of IBS in individuals seeking medical care is higher in males.[3] In an analysis of 38 studies which provided data on risk factors for developing IBS, female sex was found to be a risk factor in 19 studies; whereas, 12 found no difference in incidence between men and women, with 6 of these 12 studies from Taiwan.[3]

In an internet survey of 30,000 adults from the general Japanese population, the rates of abdominal discomfort, abdominal distension, and abdominal fullness were significantly higher in females than males with IBS-C (66.5% vs. 58.7%, $p < 0.05$; 54.7% vs. 43.6%, $p < 0.01$; 18.9% vs. 9.6%, $p < 0.01$, respectively).[22]

Diagnostic criteria, symptoms and prognosis according to sex

Irritable bowel syndrome is defined by the same symptoms in both sexes. In addition to the tendencies for higher prevalence among men presenting for care in some Asian countries mentioned above, there may be sex-related differences among the subtypes of IBS or typical symptoms. For example, although pain-related symptoms of IBS are similar in men and women, other symptoms including mucus, incomplete evacuation, distension, and scybala (hardened lumps of stool) are less common in men.[23] Among 90 patients with IBS in Iran (29 men, 45 pre-menopausal women, 16 post-menopausal women),[24] IBS-D was more common in men (44.8%), whereas IBS-C and IBS with alternating bowel habits (IBS-A) were more common in women (39.3%, 42.6%, respectively). The women had a greater severity of abdominal distension, rumbling, flatulence, and dissatisfaction with bowel functions compared to the men. The scores for quality of life (IBS-QoL) in women were significantly lower than those in men.[24]

Chronic life stress is a powerful predictor of clinical outcome in patients with IBS; however, sex does not appear to influence the prognosis in IBS.[23]

Is there association of sex with overlap of IBS with other gastrointestinal or non-gastrointestinal symptoms?

The overlap of IBS with other gastrointestinal symptoms (e.g. heartburn) or syndromes (e.g. dyspepsia) is well recognized,[25] and there is high turnover in symptom status with symptom transitions rather than total symptom resolution, suggesting a common etiopathogenesis of different functional gastrointestinal disorders (FGIDs).[26] The effect of sex was not investigated in those studies. More recently, the profiles of both gastrointestinal and non-gastrointestinal symptoms appear to be reproducible, even with different Rome criteria for IBS (Rome III and IV); however, there were no statistically significant differences regarding gender distribution.[27]

Psychosocial issues, eating disorders, stress and sex

Female patients with IBS and non-patients have similar increases in psychological distress, which correlate with gastrointestinal symptoms in about 40% of IBS.[28] In referral-based gastroenterology practice, 44% of women with IBS reported a history of abuse; these women were more likely than non-abused patients to report pelvic pain, multiple somatic symptoms, and prior surgeries.[29,30] The degree of anxiety was significantly associated with abdominal discomfort and abdominal pain, but not with abdominal bloating in female subjects with IBS-C. In contrast, the degree of anxiety was not significantly associated with abdominal bloating, discomfort, or abdominal pain in male subjects with IBS-C.[31]

Patients with FGIDs (15.7%) had eating disorders more frequently than patients with an organic gastrointestinal disease, specifically gallstones (3.1%). Risk factors for eating disorders in FGIDs were more years of formal education, psychologic distress, and female gender. Patients with FGIDs associated with eating disorders had a higher prevalence (95–99%) of elevated scores for anxiety and depression on the Hospital and Anxiety Depression Scale compared to patients with FGIDs without eating disorders (40–48%).[32]

Stress is an important factor associated with IBS. The association between early life stress (such as trauma, abuse, poverty) and IBS in adulthood is driven by female sex based in some epidemiological studies,[33] although the effect of sex was not significant in a more recent, larger study.[34] There is also an experimental basis for this observation, as sex moderates the associations between early adverse life events (EALS) and measures of centrality. There is decreased centrality of salience and emotion regulation regions with increased general EALs in females, and increased centrality in salience regions with higher physical and emotional EALs in males.[35] Similarly, there is evidence for disease and sex-related alterations in the default mode, salience, and basal ganglia networks in patients with urological chronic pelvic pain syndrome, which are moderated by EALs.[36]

Brain-gut axis and sex hormones in IBS

There is considerable evidence[37,38] linking the effects of sex hormones and stress responses on the central and autonomic nervous systems and enteric mechanisms. In the central nervous system, there are sex-related differences in pain modulation and in the brain regions activated by the same visceral stimulus. Thus, in response to rectal stimulation, women with IBS have increased activation (measured by blood flow changes) of brain structures involved

in emotional processing of pain (the limbic system) rather than the visceral cortex (e.g., insula) that is activated in men (discussed below). Kim and Kim[37] have reviewed in detail the experimental studies showing that estrogen increased pain modulation, whereas testosterone had analgesic effects, and that both estrogen and progesterone increased activity of the hypothalamic-pituitary-adrenal axis with increases in circulating levels of corticotropin-releasing hormone and cortisol; whereas, testosterone reduced stress-related ACTH release. This is associated with higher stress responses as well as anxiety and hypervigilance in women with IBS. It has been demonstrated that women experience greater clinical pain, lower pain threshold and tolerance, and more sensitivity and distress to experimentally induced pain compared to men, and there is evidence that neuroanatomical, hormonal, neuroimmunological, psychological, social and cultural aspects contribute to the differences.[39] Among these, some of the most impressive differences are neuroanatomical factors and interactions of gonadal hormones in pain-processing brain regions, which are summarized in Table 1.

In the autonomic nervous system, estrogen increases sympathetic responsiveness and progesterone reduces cholinergic responsiveness.[37] In five studies that assessed the autonomic nervous system in patients with IBS, there was uniform demonstration of increased sympathetic activity at rest or in response to stimuli such as meal ingestion or rectal distension, with inconsistent findings in parasympathetic function (reviewed in ref.[40]). There were subtle differences in autonomic functions according to gender,[41] but no differences among IBS subgroups based on bowel function.[6] Nevertheless, the observations suggest that autonomic responses to visceral pain in IBS are increased, and the relationship of female sex hormones is certainly plausible. An additional biological effect that might be expected from increased sympathetic and decreased parasympathetic (cholinergic) responsiveness resulting from effects of female sex hormones is slowing of colonic transit.

Prior reviews have documented effects of sex hormones on intestinal motor and sensory functions.[37,38] In experimental studies, estrogen tended to accelerate and progesterone to slow intestinal transit, and women with IBS-D with a low estrogen to progesterone ratio had increased serotonin levels, which may contribute to the alterations in intestinal transit. Women with IBS had increased somatic and visceral pain, and the estrogen α and β receptors modulated pain in the dorsal root ganglia. There was increased spinal neuronal activity in women with IBS. Intestinal permeability tended to be reduced by estrogen, with increased expression of tight junction proteins such as occludin. Women with IBS had increased mast cell activity in intestinal mucosal biopsies, and both estrogen and progesterone increased T-cell activity.[37,38] Finally, there is evidence that gut microbiota may be influenced by female sex hormones. For example, estrogen receptor β expression affected the gut microbiota composition, and both estrogen and progesterone had direct effects on bacterial metabolism, growth and expression of virulence factors.[37,38]

Pain perception among genders

There are definite differences in pain perception among genders. Females rate noxious somatic heat stimuli as more intense and females are better at discriminating between different pain intensities than males.[42] There are lower pressure thresholds for pain during

rectal distension among women with IBS compared to men, and the areas of the central nervous system that are activated during such colorectal distension differ between women and men.

Females have a higher tendency to respond to pain with anxiety and are more likely to disclose their symptoms to others.[43] There is a higher prevalence of abdominal pain in girls and women than males,[44] and rectal hyperalgesia in response to repetitive sigmoid stimulation is more frequent among females with IBS compared to males with IBS.[45] Women have higher prevalence of chronic musculoskeletal pain compared to men, and women over 35 years of age perceive pain in more locations than men.[46] The hyperalgesia is also associated with sex-related differences in the regional brain responses to a gut-directed stimulus. For example, there is greater stimulation of the right anterior cingulate cortex, left infragenual cingulate cortex, and amygdala in females than in males with IBS. In contrast, males have greater activation of the right dorsal lateral prefrontal cortex, insula, and periaqueductal grey area of the dorsal pons from which descending modulation impacts ascending sensory pathways.[47] Thus, male patients have greater activation of the normal visceral sensory centers during distension of the lower bowel; whereas, females have greater activation of the emotional motor system, specifically the anterior cingulate cortex, insula, and amygdala, with visceral stimulation.[47]

Colonic transit and sex

Based on a longitudinal survey of self-reported bowel functions and the previously documented relationship between hard stools and delayed colonic transit,[48] women in the general population had slower whole gut transit times, tended to report less frequent stools, and had a higher prevalence of constipation than males.[49] There was a larger inter-individual coefficient of variation in colonic transit at 24 and 48 hours in 139 healthy females (respectively 40% and 30%) compared to 72 healthy males (respectively 32% and 24%).[50] With this wide range observed in healthy women and variance observed in healthy men, there was no significant difference between healthy adult males and females, although control for BMI should be included in future assessments. Similarly, based on a study of 139 healthy adults (76 females) without gastrointestinal symptoms, normal colonic transit time for men was 0.7–2.2 days and for women 0.9–4.2 days. As a result of the greater variation among females, transit abnormalities in relation to gender-specific reference values were more common in males (30.0%) than in females (17.2%).[51] The potential impact of BMI needs to be further assessed; for example, when participants were divided into three groups (normal, overweight and obese), scintigraphically-measured colonic transit at 8, 24 and 48 hours was significantly accelerated in participants who weighed >30 kg m^2 when data were adjusted for age, gender, and subtype of lower FGID.[52]

Patients often experience aggravation of colonic transit in the luteal phase of their menstrual cycle during which progesterone levels increase. Studies have demonstrated differences in colonic transit in the follicular and luteal phases[53] or have shown no difference.[54] In fact, multiple studies (reviewed in ref. 55) failed to show clear or consistent effects of female sex hormones on gastric emptying, small bowel transit and colonic transit with either longer orocecal transit time in the luteal phases compared with the follicular phases or no

significant variation with the phase of the menstrual cycle in whole gut, orocecal, or colonic transit. This provided the rationale for a study previously conducted in 49 post-menopausal females randomized to receive, for 7 days, 400 mg/day micronized progesterone, 0.2 mg/day estradiol, combination of the two, or placebo; no significant effects were noted while on hormonal treatment or on hormone withdrawal.[55] In studies of human colonic muscle from 7 patients with slow transit constipation, there was down-regulation of contractile G proteins and up-regulation of inhibitory G proteins, probably caused by overexpression of progesterone receptors.[56]

Abdominal distension and sex

The literature on abdominal bloating and girth in IBS involves >90% females, with no data available comparing females and males with IBS. Postulated mechanisms for the abdominal distension and bloating are retention of gas (and stool), depression of the diaphragm (also called abdomino-phrenic dyssynergia),[57] excess lumbar lordosis, and voluntary protrusion of the abdomen.[58,59] Measurements of abdominal girth have demonstrated increases after ingestion of each meal and reductions postprandially over ~2 to 3 hours, presumably representing the reabsorption of fluid entering into the small intestine during the process of nutrient digestion or passage of fluid into the colon. However, it was impressive that these recordings also showed a dramatic reduction in abdominal girth while the participants were asleep.[58,59] Given the greater prevalence of rectal evacuation disorders among females, with a ratio of ~3 to 1 for symptoms of outlet delay among people in the community[60] or a ratio of 2 females to 1 male in an audit of 74 patients with rectal evacuation disorders in a single gastroenterologist's practice,[61] it is conceivable that the abdominal distension and associated bloating among female patients with IBS reflect rectal evacuation disorders often presenting in association with manifesting of IBS-C. This is supported by studies that showed rectal evacuation disorders are associated with abdominal bloating and constipation in patients with IBS and patients with eating disorders.[62,63]

Overlap of IBS with urogynecological symptoms

The overlap between IBS and urogynecological symptoms and diseases is reviewed elsewhere.[64] In summary, dysmenorrhea, dyspareunia, chronic pelvic pain, and pelvic floor tension myalgia are frequent in women of child-bearing age, and they often occur with symptoms of IBS. Up to 38% of post-menopausal women describe altered bowel functions, and symptoms of IBS-D or IBS-C are associated with menses in 34% to 95% of patients with IBS in different series. Among female patients with pelvic pain in whom diagnostic laparoscopies had been performed, 50% had IBS symptoms, and women with IBS-type symptoms were more likely to have undergone hysterectomy or other abdominal operations than controls without IBS symptoms. Urinary symptoms including urgency, nocturia, dysuria, and frequency occur commonly in females with IBS. Concurrent IBS was noted in 32.0% of men and 34.8% of women in Japan with overactive bladder,[65] suggesting that urinary and IBS symptoms may share a common mechanism, such as pelvic floor dyssynergia.

Fibromyalgia and sex and relationship to IBS

Fibromyalgia is more prevalent in females than males. Fibromyalgia and IBS frequently coexist; 32–65% of patients with IBS have fibromyalgia, and 32–70% of patients with fibromyalgia have IBS.[66,67] Women with chronic pelvic pain have a higher prevalence of fibromyalgia (4–31%) and IBS (8–41%) than the general population.[68] Fibromyalgia was associated with a 1.54-fold increased risk for IBS, but there was no difference in the prevalence of IBS between males and females with fibromyalgia.[69]

Immune activation and sex in IBS

There is evidence of immune activation including increased numbers of mast cells and proximity to nerves in the mucosal biopsies from patients with IBS. There is also evidence of significantly increased mast cells in female IBS patients, whereas CD3+ and CD8+ T cells are decreased in male patients.[70] Based on rodent studies, these effects may be directly related to gonadal hormones: mast cell degranulation is inhibited by progesterone and stimulated by estradiol,[71,72] whereas, increased T-cell-mediated activation in men may result from testosterone modulation.[73]

Serotonin metabolism, mucosal expression and genetics andsex

PET studies of the brain have shown that rates of serotonin synthesis in the human brain are significantly higher in males than in females at baseline and after acute tryptophan depletion.[74] The level of serotonin at synapses is determined by release from the source such as a neuron or enteroendocrine cell, and the reuptake process by neurons or platelets which is dependent upon the function of the serotonin transporter protein. In an extensive study of genetic control of serotonin, the following genes were evaluated: *SLC6A4* which controls the serotonin transporter protein, *S100A9* which controls calgranulin B (a granin influencing synthesis of 5-HT), and *S100A10* which controls synthesis of the protein P11. The latter protein transports members of the voltage-gated Na and K channel families to the plasma membrane and enhances expression of acid-sensing ion channels (ASICs) which are involved in pain. In addition, P11 interacts and co-localizes with 5-HT_{1B} receptors.[75] Earlier research demonstrated that there is over expression of *S100A10* mRNA in rectal and sigmoid mucosal biopsies in patients with IBS, which could potentially increase serotonin receptor functions such as activation of 5-HT_{1B} receptors.[76] There are gender differences in serotonin signaling in mucosal biopsies from the rectum of patients with IBS, specifically, increased levels of *S100A9* and *SLC6A4* and decreased *S100A10* in women with IBS-D.[75] In addition, there are significant correlations between rectal mucosal *S100A10* or *S100A8* mRNA and diarrhea measured by a gastrointestinal symptom rating score.[75] Increased *SLC6A4* would be expected to result in less 5-HT to interact with downstream receptors, e.g. 5-HT_4 receptors on intrinsic cholinergic neurons, and this could impact colonic transit due to absence of 5-HT, which is an endogenous stimulant of peristalsis.

A recent experimental study documented that female serotonin transporter (SERT)-gene knockout (KO) rats exhibit hypersensitivity to colorectal balloon distension that mimics the colonic hypersensitivity occurring in female IBS patients. In this model, increased 5-HT signaling at dorsal spine 5-HT_3 receptors was responsible for visceral hypersensitivity in female, but not male SERT-KO rats.[77]

Association of sex with germ-line DNA and gene expression in IBS

In a sample of 45,750 Swedish twins, there was no evidence of sex differences in heritability of irritable bowel syndrome.[78] Later, a genome-wide significant association of chromosome 9q31.2 (single nucleotide polymorphism rs10512344) and IBS was detected in women only, and specifically in women with constipation-predominant IBS and harder stools.[79]

An example of different gene expression by sex is illustrated by the observation that men with IBS had increased cortisol response to ACTH, a response which is blunted in women with IBS; in addition, men also had reduced glucocorticoid receptor mRNA expression in peripheral mononuclear cells,[80] a peripheral marker of central hypothalamopituitary response.

Sex differences in dietary coping with gastrointestinal symptoms

Female patients with IBS seem to be more willing to change dietary habits because of their gastrointestinal problems than men. Fatty food, wheat products, certain vegetables, dairy products, and eggs were significantly more reported to cause gastrointestinal complaints among patients with IBS compared to controls. A majority of both women and men who changed their dietary habits because of gastrointestinal problems experienced improvement in symptoms.[81]

Responsiveness to pharmacological and psychotherapeutic treatment of IBS by sex

Table 2 shows a summary of responsiveness by gender to treatment of IBS.[37] A classical example is provided by the gender-related differences in slowing colonic transit by the 5-HT_3 antagonist, alosetron, in subjects with IBS-D.[82] Unfortunately, for many medications, including antidepressants (reviewed in ref. 83), and for psychotherapeutic treatments, there have not been comparisons of efficacy among females and males. Clinical efficacy has, in fact, been documented for both males and females with alosetron, eluxadoline, and linaclotide, and with cognitive behavioral therapy.[84,85]

There appears to be greater efficacy in females with tegaserod and, in males, with cilansetron. The differences in responsiveness have not been proven to be attributable to underlying biological differences such as abnormal colonic transit or pain perception; in fact, the relative proportions of female and male participants in the trials may have impacted the observed differences in responsiveness.

Conclusion about sex effects in IBS

Biological variations in sex hormones, serotonergic mechanisms and pain pathways, psychosocial issues, and urogynecological co-morbidity (summarized in Figure 1) result in differences in presentation, and may require different treatments of IBS between female and male patients. A general theme that is impacted by most of these biological variations is the greater pain perception in females. This is manifested in the effects of sex hormones on pain sensation and by documentation in patients with IBS of the lower thresholds for visceral pain, increased activation of brain emotion-associated centers during visceral stimulation, the interaction between sex and early life event stress and pain experience, and differences in

serotonergic mechanisms, such as the greater expression of the serotonin-transporter protein to inactivate endogenous 5-HT and the greater responsiveness to the 5-HT_3 antagonist, alosetron. Future research should rigorously control for the phase of the menstrual cycle, pre- versus post-menopausal state, exposure to gonadal hormones, and early life events or adult stressors in assessing physiological measurments such as transit, pain sensation and brain imaging. At present, the factors considered here provide convincing evidence that irritable bowel syndrome is an example of a significant biological impact of sex.

Acknowledgements:

The author thanks Mrs. Cindy Stanislav for excellent secretarial assistance.

Funding Support: M. Camilleri's work in the field of IBS is supported by grant R01-DK115950 from National Institutes of Health.

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IMPACT STATEMENT

Differences related to sex in biological processes occur in patients with IBS.

Sex-related differences impact the brain-gut axis; functions related to pain perception, immune, and pelvic floor function, colonic transit, psychology, eating disorders, fibromyalgia, serotonin, and responsiveness to diverse treatments.

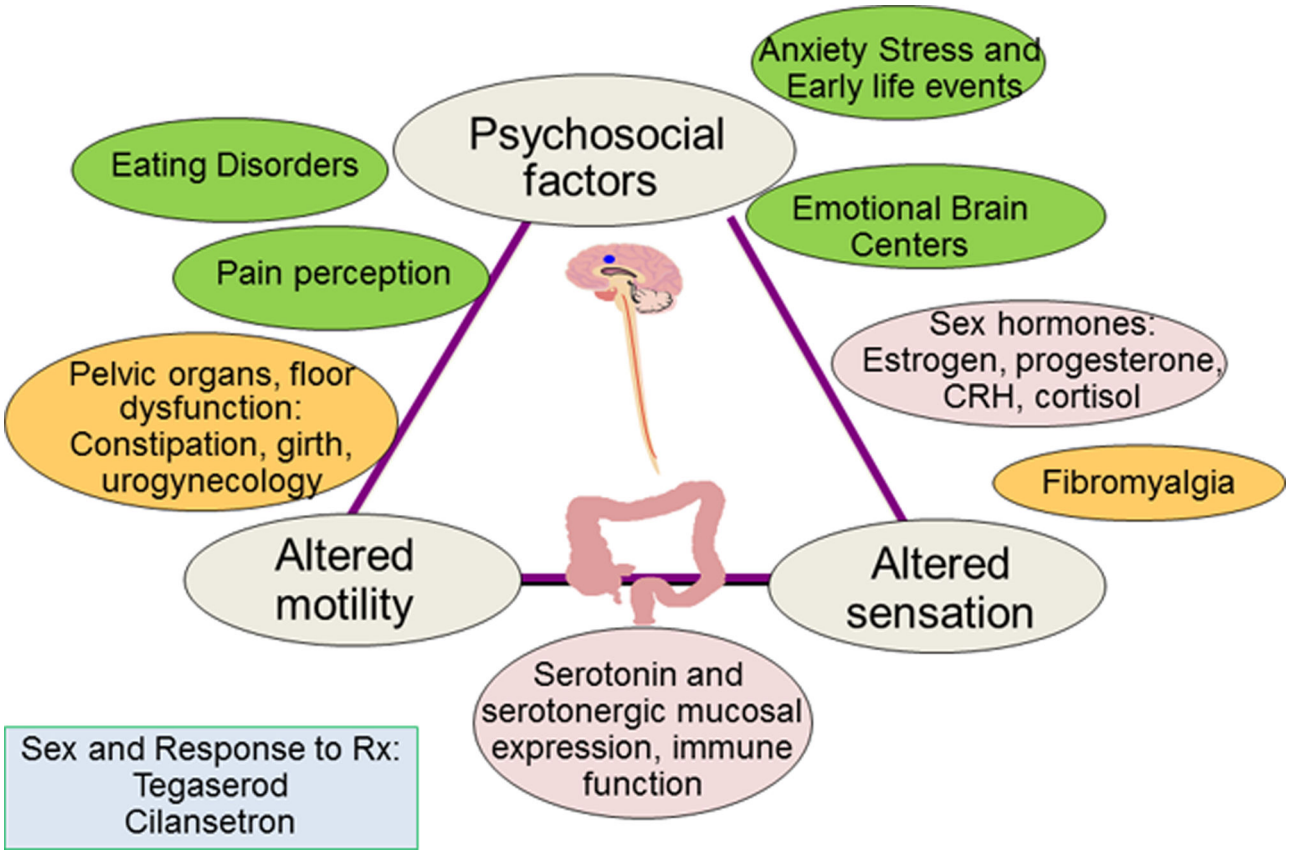

Figure 1.
Summary of sex-related differences in irritable bowel syndrome

Table 1.

Neuroanatomical Factors and Interactions of Gonadal Hormones in Pain-processing Brain Regions

A.	Neuroanatomical Factors: Brain imaging studies show sexually dimorphic activation of the anterior cingulate cortex (ACC), the insular cortex (IC) and the medial prefrontal cortex (MPC):	
	i.	Greater activation in MPC, IC and ACC in response to thermal and electrical stimuli in women than men
	ii.	Female patients with IBS exhibit much greater activation in the ventromedial prefrontal cortex, ACC and left amygdala,
	iii.	Male patients display greater activation of the PAG, right dorsolateral prefrontal cortex and insula; greater activation of the dorsal pons/PAG region on visceral stimulation results in differences in autonomic and/or antinociceptive responses to pelvic visceral stressors
B.	Interactions of Gonadal Hormones	
	i.	Hypothalamus: testosterone increases β-endorphin concentration; estrogen attenuates μ-opioid induced hyperpolarization and provokes μ-opioid receptor internalization
	ii.	Hippocampus: estradiol upregulates TRPV1
	iii.	Limbic system (thalamus, nucleus accumbens, amygdala): estradiol increases μ-opioid neurotransmitter tone
	iv.	Trigeminal ganglia and periaqueductal gray: testosterone upregulates μ-opioid receptors
	v.	Rostral ventromedial medulla: testosterone increases pain inhibitory activity

Table 2.

Summary of responsiveness by gender to treatment of irritable bowel syndrome.

Adapted from ref. 37, Kim YS, Kim N. Sex-gender differences in irritable bowel syndrome. *J Neurogastroenterol Motil* 2018;24:544–558.

Target	Drug, oral dose	Mechanism of action	Effect by Sex/gender
IBS-D	Alosetron 0.5–1mg bid	5-HT_3 receptor antagonist	Efficacy in both F and M
	Ondansetron 4–8mg q. 8h		Not assessed F vs M
	Cilansetron 2mg tid		Efficacy in M > than in F
	Ramosetron 2.5–5μg daily		Dose in M 5μg; F 2.5μg
	Colesevelam 1.875 bid	Bile acid sequestrant, ↓colon transit	Not assessed F vs M
	Loperamide 4mg…16mg/d	μ opioid agonist, ↑ IAS tone	Not assessed F vs M
	Eluxadoline 100mg bid	μ + κ opioid agonist, δ opioid receptor antagonist	Efficacy in both F and M
	Rifaximin 550mg tid * 14 d	Alters gut microbiota	Not assessed F vs M
IBS-C	Tegaserod 6mg bid	5-HT_4 receptor agonist	Efficacy in F > than in M
	Linacotide 290μg daily	Guanylate cyclase C agonist	Efficacy in both F and M
	Lubiprostone 8μg bid	ClC-2 activator	Approved for F >18y
Pain	Dicyclomine 20–40mg qid	Smooth muscle relaxant, anti-muscarinic	Not assessed F vs M
	Hyoscyamine 0.125–0.25 q.4h prn		
	Peppermint oil 0.2–0.4mL tid	Smooth muscle relaxant	