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TOPIC HIGHLIGHT

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Sex hormones in the modulation of irritable bowel syndrome

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Abstract

Compelling evidence indicates sex and gender differences in epidemiology, symptomatology, pathophysiology, and treatment outcome in irritable bowel syndrome (IBS). Based on the female predominance as well as the correlation between IBS symptoms and hormonal status, several models have been proposed to examine the role of sex hormones in gastrointestinal (GI) function including differences in GI symptoms expression in distinct phases of the menstrual cycle, in pre- and post-menopausal women, during pregnancy, hormonal treatment or after oophorectomy. Sex hormones may influence peripheral and central regulatory mechanisms of the brain-gut axis involved in the pathophysiology of IBS contributing to the alterations in visceral sensitivity, motility, intestinal barrier function, and immune activation of intestinal mucosa. Sex differences in stress response of the hypothalamic-pituitary-adrenal axis and autonomic nervous system, neuroimmune interactions triggered by stress, as well as estrogen interactions with serotonin and corticotropin-releasing factor signaling systems are being increasingly recognized. A concept of "microgenderome" related to the potential role of sex hormone modulation of the gut microbiota is also emerging. Significant differences between IBS female and male patients regarding symptomatology and comorbidity with other chronic pain syndromes and psychiatric disorders, together with differences in efficacy of serotonergic medications in IBS patients confirm the necessity for more sex-tailored therapeutic approach in this disorder.

Key words: Brain-gut axis; Irritable bowel syndrome; Microbiota; Pain modulation; Sex hormones

Core tip: Recent clinical and experimental findings support the modulatory actions of sex hormones exerted at different levels of the brain-gut-microbiota axis in irritable bowel syndrome (IBS). Sex hormones may influence peripheral and central regulatory mechanisms contributing to the alterations in visceral sensitivity, motility, permeability, and immune activation of intestinal mucosa. A new concept of "microgenderome" is emerging based on the observations that the gender bias present in numerous diseases may be reinforced by the commensal microbiota of the host. Significant sex differences in epidemiology, symptomatology, and treatment outcome in IBS indicate the necessity for sex-tailored therapeutic approach in this disorder.

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INTRODUCTION

Sex hormones, in particular estrogens, play a significant role in the physiology and pathology of the gastrointestinal (GI) tract including regulation of motor and sensory function[1,2]. Irritable bowel syndrome (IBS) is a GI sensory-motor disorder characterized by abdominal pain or discomfort associated with a change in bowel habits[3]. The role of gonadal hormones in symptomatology and pathophysiology of IBS is being increasingly recognized based on the female predominance as well as the correlation between IBS symptoms and hormonal status during menstrual cycle phases, pregnancy or menopause[4]. Sex differences in stress and pain response are considered as crucial factors in the pathogenesis of functional GI disorders[4,5]. Sex hormones influence peripheral and central regulatory mechanisms of the brain-gut axis involved in the pathophysiology of IBS contributing to alterations in visceral sensitivity, motility, permeability, and immune activation of intestinal mucosa[4,6,7]. Among numerous interactions of sex hormones with other neurotransmitters, estrogen interactions with serotonin and corticotropin-releasing factor (CRF) signaling systems play a pivotal role[8,9]. Estrogens can also modulate neuroimmune interactions triggered by stress *via* the brain-gut axis[10]. Recently, the gut microbiota has been also recognized as an important element in the bi-directional communication along the brain-gut axis through neural, immune, and endocrine pathways[11,12]. In the present article we will review recent clinical and experimental findings supporting the modulatory effect of sex hormones, in particular estrogens, on different levels of the brain-gut-microbiota axis in IBS and their clinical implications regarding the symptomatology, pathophysiology and treatment of IBS.

SEX AND GENDER DIFFERENCES IN IBS PREVALENCE AND SYMPTOMATOLOGY

In Western countries the female-to-male ratio among non-patient population of IBS sufferers is 2:1[13]. Within the patient population in primary or tertiary care settings females outnumber male patients by 3:1 to 5:1, respectively[13-15]. However, in many Eastern countries such as India, China and South Korea, the female predominance among IBS patients is not observed[16]. Likewise, results of recent meta-analysis studies in South Asia, South America, or Africa confirmed that IBS prevalence was not significantly higher in women, compared to men[17]. Therefore gender-related and socio-cultural differences in health care-seeking behavior are suggested to also account in IBS symptoms reporting[18]. Further epidemiologic studies from different world regions are needed to elucidate the complex interactions between genetic, environmental, psychological and/or cultural factors that may contribute to sex differences in IBS symptoms[19,20].

Additionally, as the prevalence of IBS subtypes varied according to gender[17], the dominating subtype of IBS in different countries may also affect the male-to-female ratio. Women with IBS, compared to male patients, are more likely to report constipation, bloating, severe abdominal pain, and feeling of incomplete evacuation, while men with IBS more frequently complain of diarrhea-associated symptoms[17,19,21]. In fact, earlier studies indicate that women have slower colonic transit in comparison with men[22,23]. The results of the recent study by Tang *et al*[24] conducted in Chinese population confirmed significant differences between female and male IBS patients in their rating of abdominal pain/discomfort with regard to severity and duration, but not frequency of pain attacks. Interestingly, sex differences in dietary coping with GI symptoms have also been reported[25]. Female IBS patients seem to be more willing to implement nutritional behavior changes alleviating the GI problems than men, although both men and women could benefit similarly from these changes[25].

Cain *et al*[26] reported higher GI symptoms (pain, distension, bloating, intestinal gas) in postmenopausal women than in men, but the greatest differences in the overall symptom reporting between men and women were associated with somatic symptoms such as joint and muscle pain. This gender-related difference was most prominent when postmenopausal women where compared to men. Gender differences were much weaker for psychological and emotional symptoms except for fatigue, sleep disturbances and stress[24,26]. Noteworthy, there is a wide spectrum of chronic pain disorders frequently overlapping with IBS namely fibromyalgia, migraine headache, chronic pelvic pain, interstitial cystitis, and chronic fatigue syndrome. These diseases are also characterized by female predominance with a correlation between their symptoms and hormonal status[27-29]. In addition, women with IBS, more frequently show comorbidity with affective or mood symptoms including anxiety and depression as compared to women without IBS[30]. There are also reports indicating that women with IBS exhibit more anxiety and depressive symptoms compared to men with IBS[24,26]. Sex differences in the prevalence of concomitant somatic symptoms, as well as anxiety and depression may significantly contribute to the greater impairment of quality of life in female patients and affect treatment results[24,31].

Sex-related difference in IBS prevalence emerges around the time of puberty and increases during the early adult years. Women are suffering from IBS most commonly in the late teenage to mid forties, additionally suggesting the role of reproductive hormones in the pathophysiology of the disorder. The incidence of IBS in women steadily declines with age and approaches the rate observed among men by the 7th decade of life[32]. By contrast, the prevalence of IBS among males is fairly constant within the age range of 20-70 years[32].

CORRELATION BETWEEN IBS SYMPTOMS AND HORMONAL STATUS

Menstrual cycle

The menstrual cycle in women is divided into three

Table 1 Correlation between hormonal status and irritable bowel syndrome symptoms expression[36]

Status	Hormone levels	IBS and pain related symptoms expression	Ref.
Late luteal phase (premenses)	Rapid decline in estrogen and progesterone levels	Exacerbation of bowel symptoms Increased bloating	[33,34]
Menstruation (menses)	Lowest levels of estrogen and progesterone	Exacerbation of bowel symptoms Increased abdominal pain/discomfort Lower rectal sensitivity threshold	[34,35,37,38,40]
Dysmenorrhea	Disturbances in hormonal interactions at different regulatory levels (lower progesterone level)	Exacerbation of bowel symptoms	[41]
Pregnancy	Physiological hyperestrogenemia and hyperprogesteronemia	Reduced pain sensitivity and alleviation of many chronic pain syndromes Exacerbation of constipation (prolonged gastrointestinal transit)	[27,51,73]
Menopause	Decline in ovarian hormones	Decrease in IBS incidence High prevalence of constipation and somatic discomfort syndromes	[26,53,54]
Oral contraceptives	Estrogen and progestin administration	Reduced abdominal symptoms at menses	[55]
Hormone replacement therapy	Estrogen (and progesterone) supplementation	Increased prevalence of IBS in postmenopausal women during HRT Prolongation of IBS symptoms to a later age	[58]
Oophorectomy	Ovarian hormone deficiency	Exacerbation or occurrence of gastrointestinal symptoms after gynecological surgery	[60]
Men with IBS	Lower level of luteinizing hormone in middle-aged men Elevated level of sex hormone-binding globulin in young men	Generally more prevalent diarrhea (compared to women with IBS)	[66,70]
Transsexual women (male-to-female subjects)	Estrogen/anti-androgen treatment	Development of chronic pain including visceral pain	[72]

IBS: Irritable bowel syndrome; HRT: Hormone replacement therapy.

phases: the follicular (proliferative) phase, ovulation, and the luteal (secretory) phase. Estrogen levels are increasing during the midfollicular phase and then drop precipitously after ovulation. This is followed by a secondary rise in estrogen levels during the midluteal phase with a decrease before menstruation. The secondary rise in estradiol parallels the rise of serum progesterone and 17-hydroxyprogesterone levels[33].

Dynamic changes in ovarian hormones during menstrual cycle can modulate GI contractility, transit, secretion, visceral sensitivity, and immune function at multiple target sites, including those located in the periphery and the brain[3]. Clinical studies indicate that declining or low ovarian hormone levels in women (such as during menses) may contribute to the occurrence or exacerbation of GI symptoms, including abdominal pain or discomfort, altered bowel habits and bloating that varies across the menstrual cycle phases (Table 1)[34-37]. Rectal sensitivity thresholds have been shown to be significantly lower in IBS patients at menses relative to those at other cycle phases indicating that IBS symptoms experience may be modified by ovarian hormone status[38]. Also in animal studies it has been shown that both visceral and somatic sensitivity vary over the rat estrous cycle and that high levels of ovarian hormones (proestrus/estrus stages) are associated with enhanced sensitivity[39]. Therefore the menstrual cycle provides a natural model to explore the effects of ovarian hormones on the bowel function.

Approximately one third of otherwise asymptomatic women experience GI symptoms at the time of menstruation[34]. About 40% of women with IBS report influence of the menstrual cycle on their symptoms[35]. Whitehead *et al*[37] found that in women with functional bowel disorders (FBDs), including IBS, bowel symptoms seem to be affected by menstruation to a greater degree than in women without FBDs, suggesting that IBS women may respond differently to the fluctuations in the ovarian hormones. Variation in GI symptoms during the menstrual cycle can be related to motor disturbances and/or a change in perception of colonic motor events, as well as alterations in colonic epithelial barrier and mucosal immunity[10,40].

IBS female patients are more likely to report dysmenorrhea and premenstrual distress syndrome than those who do not suffer from IBS[41-43]. Moreover, IBS patients with dysmenorrhea report noticeably more GI symptoms than non-dysmenorrheic women[41]. In a 10-year follow-up-study conducted in Iceland it has been shown that IBS female patients with dysmenorrhea were twice more likely to have increased symptoms compared to IBS patients without dysmenorrhea[43].

A significant connection between IBS and endometriosis has also been reported[43,44]. Additionally, polycystic ovary syndrome (PCOS), the most common female endocrine disorder affecting up to 10% of reproductive-age women characterized by chronic anovulation and hyperandrogenism, is associated with the increased prevalence of IBS[45-47]. Interestingly, IBS coexisting with PCOS was associated with a higher BMI and percent body fat when compared to PCOS alone[45]. The relationships between obesity, hormonal status and IBS require further investigation, particularly in the context

of obesity being linked with increased inflammatory mediators and in the light of recent reports on the GI dysbiosis[46,48].

Pregnancy

Pregnancy is characterized by high ovarian hormones levels as well as an increase in opioid-mediated antinociception[3,49]. Little is known, however, regarding IBS symptoms and pregnancy. Many chronic pain syndromes frequently associated with IBS, like migraine headache for example, are alleviated during the time of pregnancy[27]. Similarly, in rodents high ovarian hormones levels during pregnancy reduce somatic and visceral pain sensitivity[50]. During the time of the physiological hyperestrogenemia and hyperprogesteronemia a prolonged GI transit is also observed[51]. Additionally, numerous psychological variables affecting the autonomic nervous system (ANS) may trigger or modulate symptoms reported in pregnant women[52].

Menopause

Data concerning the impact of the menopause transition on IBS patients remain inconsistent. Although the decline in ovarian hormones may induce or exacerbate GI symptoms, generally, in postmenopausal period, the incidence of IBS decreases significantly[53-55]. However, according to some recent data, IBS symptoms severity may increase after menopause as well[43]. Cain *et al*[26] found that various GI symptoms were reported more frequently by postmenopausal women compared with men, but these differences were not significant when controlled for age. In one study, gas and excessive flatulence were more prevalent in post- than premenopausal healthy women[53].

Hormone supplementation

Premenopausal healthy women taking oral contraceptives (OCs), monophasic or triphasic preparations, report a typical increase in GI symptoms at menses[55]. However, women with IBS taking OCs, which contain both estrogen and progestin, appeared to have reduced levels of abdominal symptoms compared with IBS women not taking OCs[55]. At the same time, the pattern of GI and non-GI symptoms over the menstrual cycle was similar in female patients with IBS, regardless of OCs use or the predominant bowel pattern[55]. Noteworthy, in women with dysmenorrhea that may coexist with IBS, OCs often reduce the symptoms[15]. Recently, Bird *et al*[56] reported an increased risk for development of IBS with drospirenone. Drospirenone is a synthetic progestin approved in combination with ethinyl-estradiol as an OC. Although it was designed as an antimineralocorticoid steroid, it exhibits antiandrogen activity[56]. In another study evaluating the effect of hormone supplementation on IBS symptoms, the therapeutic efficacy of gonadotropin-releasing hormone agonist (leuprolid) in female patients with menstrual cycle-related symptoms has been reported[57]. However, the use of this medication is limited by its side effects[57].

Based on the recent meta-analysis, there are insufficient data to determine the exact effect of hormone supplementation during menopause on IBS symptoms[19]. In postmenopausal women, hormone replacement therapy (HRT) has been reported to be associated with the increased prevalence of IBS. HRT may prolongs IBS symptoms to a later age or even induce changes in GI function in females not previously affected[58]. One of the confounding factors may be related to the fact that women with IBS are more likely to report various pre- and postmenopausal symptoms, and thus may be prescribed HRT to a greater degree. However, Ruigómez *et al*[58] have shown that both current and past users of HRT presented an increased risk of IBS compared to non-users, even after adjusting for comorbidity and consultation pattern. This increased risk was irrespective of treatment duration, regimen or route of administration of HRT[58].

Gynecological surgery

There are few data concerning the prevalence of oophorectomy or hysterectomy in IBS female patients, mostly because these surgical procedures are excluding factors in the studies of IBS patients. However, it has been reported that the rate of hysterectomy is about twice higher in women with IBS compared to controls[59]. It is conceivable that IBS patients, because of the chronic abdominal pain, are more likely to be qualified for various surgical procedures (not only gynecological, but also GI surgery like cholecystectomy and appendectomy)[59]. In fact, in a number of women, GI symptoms emerge for the first time after gynecological surgery[60]. Preclinical studies however remain controversial. There is indeed evidence in mice that ovariectomy generates a slow developing and persistent hyperalgesic state localized to the abdomen, lower limbs and abdominal viscera, which is reversed by estrogen supplementation[61,62]. In contrast, in rats, ovariectomy decreased the magnitude of the visceromotor response to colorectal distension compared with cycling rats[63] and abolished restraint stress-induced visceral hypersensitivity[64]. The sensitivity to colorectal distension and the influence of stress on visceral pain were restored by estrogen replacement at a dose comparable to the proestrus level[65].

Male sex hormones

Most of the explanations of sex-related differences in IBS have focused on the concept that women might be more susceptible, while less attention has been given to the concept that male hormones may be protective against pain disorders including IBS[66]. Androgens, higher in males than females, appear to protect against the development of chronic pain disorders in humans, and testosterone exerts an analgesic effect in experimental pain models, in both men and women[67-69]. Differences in androgen levels, their receptors as well as sites of action may play a role in the sex difference in the risk of developing chronic pain disorders. There are only few reports concerning the role of sex hormones in male

patients with IBS[67,70,71]. Houghton *et al*[66] found that testosterone levels, although similar in the patient and control groups, correlated negatively with perceptual thresholds of rectal distension and overall well-being in IBS patients. In the same study it was found that middle-aged male IBS patients tended to have lower levels of luteinizing hormone compared with male control subjects[66]. Kim *et al*[70] have also reported that the sex hormone status in young male patients is different from that of older male patients and that an elevated sex hormone-binding globulin level might play a key role in the pathophysiology of IBS in young men. Interestingly, a highly significant reduction in male-trait scores in men with IBS has been confirmed[71]. Another unique model to study the relationship between sex hormones and chronic pain was proposed by Aloisi *et al*[72] who evaluated the results of sex-crossed hormone administration in transgender subjects. About half of the female-to-male subjects treated with testosterone reported a significant improvement of the chronic pain (*e.g.*, headache) present before the treatment. Conversely, about one-third of the male-to-female subjects receiving estrogen/anti-androgen treatment developed chronic pain including headaches, breast and musculoskeletal pain, and in some cases visceral pain as well[72]. These findings support experimental and clinical data suggesting that sex steroid hormones play a crucial role in pain perception and modulation.

SEX HORMONE MODULATION OF THE BRAIN-GUT AXIS AT THE CENTRAL NERVOUS SYSTEM LEVEL

Estrogens

The abundant distribution of estrogen receptors (ERs) at all levels of the brain-gut axis, including the central nervous system (CNS), spinal cord, and the enteric nervous system supports the multiplicity of neuronal action[73]. There are two subtypes of ERs: ER-α and ER-β. Estrogens, similarly to progesterone and testosterone, exert their function by binding to either specific intracellular (nuclear) receptors that act as ligand-dependent transcription factors (classical mechanisms) or membrane-bound receptors (mERs) that stimulate several signal transduction pathways (non-classical mechanisms). The family of nuclear receptors mediate rather slow genomic action of estradiol resulting in enhancement or repression of gene transcription and thus protein synthesis alterations. In contrast, mERs are involved in the rapid action of estrogens related to the activation of various protein-kinase cascades and phosphorylation of proteins, but estrogenic rapid signaling can also occur by recruiting intracellular pathways that can act *via* the genome through phosphorylated cyclic adenosine monophosphate (cAMP) response element protein (pCREB) and intermediate early genes[74]. In addition to the well described G protein-coupled receptor (GPR30), multiple mERs have recently been discovered, such as the classical nuclear ER-α and ER-β, ER-αΔ4, ER-X and mER-Gαq[74-76].

ERs are spread throughout the brain, including the amygdala, hypothalamus, pituitary, hippocampus, cerebral cortex, mid-brain, and brain stem, providing neuroanatomical support for potential numerous target sites of estrogen actions on neurocognitive processes[73,77]. Based on the results of brain imaging studies, greater responsiveness of emotional arousal circuits in relation to visceral pain has been implicated as induceing central mechanisms of pain amplification in IBS, with female subjects showing greater response than male subjects[78]. Recent results confirmed sex differences in emotion-related cognitive processes and functioning of brain networks including the prefrontal regions, cingulate, insula, and amygdala in IBS and healthy control subjects[79].

Estrogens may act in the CNS through multiple pathways modulating production and action of neurotransmitters, influencing electrical excitability and synaptic function, and changing the morphological features of neural elements involved in the function[77,80,81]. Estrogens have been documented to exert differential, sometimes opposite effects on pain. Clinical and experimental data indicate that both analgesic and hyperalgesic responses can be induced by estrogens depending upon the experimental conditions[67]. Estrogens were shown to enhance neuronal system activities during development and in adult life, for instance through the hippocampal neuronal circuits involving acetylcholine, glutamate and brain-derived neurotrophic factor[82]. Noteworthy, elevated levels of estrogens in fertile women have been associated with the increased number of μ-opioid receptors in the brain regions related to pain processing[68]. There is accumulating evidence that estrogens have a significant impact on neuronal plasticity-related process and ameliorate recovery after chronic stress (Table 2)[73].

Estrogens may also contribute to the important sex differences in the stress-related hypothalamic-pituitary-adrenal (HPA) axis response that have been documented in a number of clinical and experimental studies[83]. The menstrual cycle phases, menopausal status and pregnancy have been shown to affect the HPA axis as well as ANS functions[5]. Women between puberty and menopause usually show lower HPA axis and autonomic responses to psychological stressors than men of the same age[84]. However, the HPA axis response to psychological stressors is higher in the luteal phase, when post-stress free cortisol level approaches that for men[84]. CRF is a key mediator of the HPA axis and the brain-gut axis response to stress at both central and peripheral levels[9,85,86]. The co-localization of ER-α with CRF receptors in the hypothalamus represents one of the possible neuroendocrine interactions between CRF signaling pathways and estrogens[87]. Importantly, activation of both receptors ER-α and ER-β has been shown to stimulate *CRF* gene expression in the hypothalamic paraventricular nucleus (PVN)[83,88]. Additionally, estrogens induce also an increase in glucocorticoid receptor expression in the amygdala[88]. In the recent functional magnetic resonance imaging study, it was demonstrated that significant sex differences in brain activity in stress

Table 2 Sex hormone modulation of the brain-gut-microbiota axis

Level of the brain-gut-microbiota axis	Estrogen	Progesterone	Testosterone
Central nervous system	Analgesic or hyperalgesic effect[67] Excitatory action on neurons[72] Estrogen-induced increase in the number of μ-opioid receptors[68] Enhancement of serotonergic postsynaptic responsiveness in the brain[8] Central interaction with CRF signaling pathways-modulation of stress responsiveness[87,89]: Stimulation of *CRF* gene expression in PVN[83] Increase in glucocorticoid receptor expression in the amygdala[83] Influence on neuronal plasticity-related processes[73]	Activation of the γ-aminobutyric acid (GABA) receptors, major inhibitory receptors in the brain[77] Neuroprotective action in the hippocampus[80]	Analgesic effect[72] Inhibition of stress-induced ACTH release[103]
Autonomic nervous system	Attenuation of sympathetic responsiveness[108]	Reduced cholinergic responsiveness[5]	Regulation of parasympathetic tone[110]
Enteric nervous system/ Gut immune system	Expression of estrogen receptors in enteric neurons, regulation of neurogenic reflexes[73] Activation of colonic NK1 receptors in stress-induced visceral hypersensitivity[64] Augmentation of mast cells secretion[118] Effects on both pro- and anti-inflammatory pathways[113] Peripheral interaction with CRF signaling pathways, modulation of colonic motor and sensory responses to stress[87] Regulation of 5-HT3 receptor expression in rat colon[120] Regulation of secretory and absorptive function of gastrointestinal epithelial cells[128] Enhanced expression of trans-membrane tight junction protein in non-inflamed colon[124] Decreased production of proinflammatory cytokines in experimental colitis in female rats[125,126]	Inhibition of gastrointestinal motility[130] Inhibition of visceral signaling following colonic inflammation[100] Inhibition of mast cells degranulation[131] Immunosuppressive action related to inhibition of NFκB activation in macrophages[133]	Stimulation of smooth muscle contractions[135] Decreased production of proinflammatory mediators inducing visceral hyperalgesia[69,136] No effect on mast cells degranulation[137] Decreased TLR4 expression of macrophages and monocytes[138]
Gut microbiota	ER-β expression affects the gut microbiota composition[143] Microbial β-glucuronidase activity determines estrogens deconjugation enabling their reabsorbtion *via* enterohepatic circulation[146] Direct effect on bacterial metabolism, growth and expression of virulence factors[132]	Direct effect on bacterial metabolism, growth, and expression of virulence factors[132]	Reversible 17β reduction of androgens may regulate testosterone level[148] Commensal microbiota-dependent testosterone production protects against autoimmune disease in mice[149]
	Bacterial hydroxysteroid dehydrogenase regulates the balance between active and inactive steroids[132]		

ACTH: Adrenocorticotropic hormone; CRF: Corticotropin-releasing factor; NFκB: Nuclear factor κB; PVN: Paraventricular nucleus; TLR4: Toll-like receptor 4.

response circuitry were dependent on women's menstrual cycle phase[89]. In addition, chronic treatment with estrogens modulates brain circuitry responsive to stress[90]. Furthermore, administration of estradiol and progesterone directly to the amygdala in rats increases pain response to visceral stimulation suggesting that an amygdala-dependent mechanism may be responsible, at least in part, for the exacerbation of visceral symptomatology in females[91]. A recent meta-analysis by Tillisch *et al*[92] points to the amygdala, a brain region known to facilitate HPA axis output, as one of the most consistently activated areas following rectal stimulation in IBS patient compared with controls. Of significance, the activation of the amygdala by corticosterone eliminates spontaneously occurring differences in visceral and somatic pain perception in cycling female rats, resulting in visceral hypersensitivity during metestrus/diestrus, and increased somatic sensitivity during both metestrus/diestrus as well as proestrus/estrus[39]. This observation could explain the lowered pain thresholds and higher incidence of somatic pain observed in women with IBS[39].

Childhood trauma (early adverse life event, EAL) is associated with changes in HPA axis responsiveness in IBS[93]. Dysregulation of the HPA axis in IBS patients has been related to blunted adrenocorticotropic hormone (ACTH) levels and enhanced cortisol response to visceral stimulation[94]. However, little is known on sex-differences in EAL-induced visceral pain. Interestingly, sexually dimorphic effects of unpredictable EAL on visceral pain behavior in a rodent model has been demonstrated[95]. Female rats exposed neonatally to different pairings of an odor and shock developed visceral hypersensitivity in adulthood, while in contrast, in male rats, visceral sensitivity was not significantly different after EAL. Visceral sensitivity following unpredictable EAL was reversed by ovariectomy and reestablished by estradiol

replacement. These data suggest estrogen-mediated pivotal mechanisms in maintaining visceral hypersensitivity[95].

The serotonergic system represents another potential contribution to sex differences in pain modulation[3,8]. In the CNS, serotonin (5-HT) generally has been associated with descending pain inhibition, whereas in the periphery, 5-HT is an inflammatory mediator and is generally pronociceptive and prokinetic. Estrogens enhance serotonergic postsynaptic responsiveness in the brain[8]. Additionally, estrogens enhance 5-HT synthesis in most part of the brain by increasing expression of the enzyme tryptophan hydroxylase and decreasing the expression of the serotonin re-uptake transporter[96]. The serotonergic and reproductive endocrine systems are also prominently involved in both the regulation of mood and behavioral states. In addition, interactions between these systems have profound implications for the etiology and treatment of anxiety disorders[97]. A growing body of evidence also indicates sex-dependent differences in serotonin-related genetic polymorphisms in IBS patients[98], particularly with regard to anxiety and depressive disorders more common in women with IBS[99].

Progesterone

The role of progesterone in sex-related differences in pain modulation is less clear. Progesterone activates intracellular receptors to regulate genomic processes, and also affects cell membrane receptors, especially in neurons[100]. Membrane progesterone receptors present in the hippocampus were suggested to contribute the neuroprotective action of the hormone[80]. At the CNS level, progesterone action seems to be dependent on the activation of the γ-aminobutyric acid receptors that are major inhibitory receptors in the brain[101].

Androgens

While estrogens are commonly indicated as CNS stimulant, androgen receptor-mediated actions are often related to CNS inhibition, which may underlie the lower incidence of many forms of chronic pain in men[72]. Androgens participate in the regulation of the HPA axis response to chronic stress and the autonomic circuitry[102]. Optical and electron microscopic immunocytochemical studies in rodents have revealed that the distribution of androgen receptors is overlapping with that of ER-α, ER-β, as well as progesterone receptors in three major autonomic regions in the brain: the rostral ventrolateral medulla, nucleus of the solitary tract and PVN[80]. In male rats, testosterone inhibits the acute restraint stress-induced ACTH release[103] that, ultimately, may impact on other brain stress-related CRF-mediated influence on colonic motility and visceral pain[9].

SEX HORMONE EFFECTS ON THE AUTONOMIC NERVOUS SYSTEM

Estrogens

Estrogens influence also nociceptive pathways at the level of primary afferent nerves and spinal cord projections[104]. A direct involvement of ERs in nociceptive transmission is possible *via* their activation of enkephalin synthesizing cells in the superficial laminae of the spinal cord[105]. Additionally, estrogens modulate the responsiveness of primary vagal afferents neurons to substance P and the activation of glutamate receptors involved in the afferent pain pathways[40]. Spinal estrogen receptors ER-α and ER-β have been also shown to contribute to the facilitation of N-methyl-D-aspartate-dependent colon-to-urethra cross-organ reflex sensitization, which is presumed to underlie pelvic viscero-visceral referred pain[106].

Autonomic dysregulation in response to a visceral stressor is an objective physiologic correlate in IBS[107]. Tillisch *et al*[108] reported gender differences in the ANS reactivity to colorectal distension in IBS patients, with men demonstrating increased sympathetic nervous system activation and decreased parasympathetic activation compared to women. There are also data indicating menstrual cycle-linked differences in the ANS tone that are likely to result from estrogen exposure, and its attenuating influence on sympathetic responsiveness[109]. Furthermore, many other chronic pain syndromes, frequently coexisting with IBS can be also related to autonomic disturbances[28].

Progesterone and androgens

Progesterone has been shown to reduce cholinergic responsiveness[5]. However, little is known about the effect of testosterone on the ANS. Recently, it has been noticed that testosterone deficiency is accompanied by a decrease in basal parasympathetic tone and reduced baroreflex sensitivity in men with heart failure[110].

SEX HORMONE ACTIONS AT THE ENTERIC NERVOUS AND GUT IMMUNE SYSTEMS

Estrogens

Within the enteric neurons of the colon, where both CRF receptor subtype 1 (CRF_1) and ERs are expressed, interactions between CRF signaling pathways and estrogens participate in the stimulation of the colonic motor function[90]. Additionally, a local paracrine/autocrine pro-inflammatory action by CRF_1 receptor activation was reported in several models of intestinal inflammation both *in vitro* and *in vivo*, as well as the up-regulation of CRF and CRF_1 expression in immune cells of the human colonic lamina propria in response to inflammation[86].

There is compelling evidence suggesting an up-regulated gut immune function in patients with IBS, particularly with post-infectious IBS[111]. Gastrointestinal inflammation seems to be strongly modulated by stress, especially in IBS patients being characterized by enhanced stress responsiveness[15]. Important sex-related differences in IBS patients related to neuroimmune inter-

actions have been suggested[71,112]. Female sex is an independent risk factor for developing postinfectious IBS[3]. The following observations support sex differences in immune response: females produce stronger cellular as well as humoral immune reaction, have a greater resistance to bacterial infections, and are more likely to develop autoimmune diseases compared to men, symptoms of which depend on hormonal status[113]. Estrogens may influence both pro- and anti-inflammatory pathways. The effect of estrogens in inflammatory responses has been found extremely complex and dependent on the estrogen level, the cell type, specific inflammatory factors, the type of tissue that is inflamed, the time course of the inflammatory response (*e.g.*, acute *vs* chronic), and the time point at which estrogen exposure occurs[113]. In an experimental model, estrogens contributed also to the colonic neurokin-1 receptor-mediated effects of stress-induced visceral hypersensitivity to colorectal distension[64].

Mast cells represent another crucial link in sex-dependent neuroimmune interactions as they co-express CRF and sex hormone receptors[114-116]. The number of colonic mucosal mast cells was found to be higher in female compared to male IBS patients[10]. Mediators released by activated mast cells, characterized by extensive anatomical and functional communication with intrinsic and extrinsic nervous system of the gut, evoke visceral hypersensitivity and increase mucosal permeability[117]. Notably, mast cells are involved in many other disorders, frequently overlapping with IBS such as fibromyalgia, interstitial cystitis, chronic fatigue syndrome and migraine, all of which occur more often in women, are exacerbated during ovulation and reduced during pregnancy[10]. These sex-related differences in the prevalence and severity of chronic pain disorders could be related to the fact that mast cells express progesterone and estrogen receptors[10]. Estradiol has been shown to augment mast cells secretion, whereas tamoxifen (an estradiol receptor antagonist) inhibits this function[118].

The serotonergic system at the peripheral level may also contribute to sex differences in modulation of GI motility, secretion and sensitivity[3,8]. Fluctuations in estrogen levels during ovarian cycle cause predictable changes in 5-HT system in women[8]. Moreover, 5-HT concentration varies with sex and menstrual status in patients with diarrhea-predominant IBS[119]. Experimental studies indicate that colonic 5-HT_3 receptor gene expression is increased in ovariectomized rats exposed to restraint stress and restored with hormone replacement after ovariectomy[120]. Recently, Galligan *et al*[121] proposed serotonine transporter (*SERT*) gene knockout (KO) rats as a new interesting model for studying interactions between serotonin, sex, and visceral sensation. SERT KO female rats display an increased colonic extracellular serotonin associated with visceral hypersensitivity and hyperexcitability of colon projecting sensory neurons, which is not observed in male SERT KO rats[121]. Gender difference has been also shown in SERT activity and serotonin concentration in platelets of IBS patients[122].

Estrogen-dependent modulation of the intestinal barrier function is another component in sex-related differences in IBS. It has been well established that stress involving the activation of CRF_1 receptors alters intestinal barrier that appears to be a prerequisite for the development of visceral hypersensitivity in both human and rodents[6,123]. In the colon, ERs signaling enhances expression of trans-membrane thigh junction proteins in non-inflamed conditions[124], and decreases production of proinflammatory cytokines in experimental colitis[125,126]. In human, acute experimental stress evokes a differential gender-dependent increase in intestinal macromolecular permeability[127]. A significant increase in albumin permeability in healthy women, but not in men, could explain enhanced female susceptibility to IBS[127].

Additionally, ERs are localized on the epithelial cells throughout the GI mucosa and may affect secretory and absorptive functions[37,128,129]. The fluid retention that occurs in females during the cycle may be associated with the extra-nuclear action of estrogen that can stimulate calcium entry into colonic epithelial cells as well as suppress c-AMP-dependent chloride secretion in the distal colonic epithelium in females only, both in rats and humans[128].

Progesterone and androgens

At the peripheral level progesterone has been suggested to influence both visceral sensitivity and motility *via* prostaglandins[100]. Overexpression of progesterone receptors in colonic muscle in women with slow transit constipation is associated with lower levels of prostaglandin $PGF_{2\alpha}$ and tromboxane A that cause muscle contraction, and higher levels of PGs that cause muscle relaxation (such as PGE_2)[130]. Progesterone may also inhibit estrogen-dependent mast cells degranulation[131]. Progesterone receptors have been identified in epithelial cells, granulocytes, macrophages, and lymphocytes[132]. Progesterone is known to exert an immunosuppressive action as it inhibits the activation of nuclear factor (NF)κB and increases the expression of the suppressor of cytokine signaling protein (COS1) in macrophages[133].

Testosterone and its active metabolite 5α-dihydrotestosterone are potent modulators of colonic motility by stimulating smooth muscle contractions through non-genomic calcium sensitization pathways[134]. In the urethral calculosis model of visceral pain, Aloisi *et al*[135] did not find any significant effect of testosterone on visceral pain. However, there is growing body of evidence that androgens may contribute to the modulation of visceral pain by decreasing pro-inflammatory mediators that participate in the development of hyperalgesia[69,136]. Apart from female sex hormone receptor expression, mast cells also express androgen receptor, however, testosterone treatment had no effect on mast cell degranulation[137]. Testosterone decreases also the expression of macrophage and monocyte Toll-like receptor 4, which is involved in the activation of the innate system response to pathogen challenge[138].

INTERACTIONS BETWEEN SEX HORMONES AND THE GUT MICROBIOTA

The increasing knowledge of the role of microbiota in health and disease state has shed a light on the critical role of the enteric microbiota, both commensal and pathogenic organisms, in regulation the brain-gut axis. This has consequently led to the coining of a new term: the brain-gut-enteric microbiota axis[11]. The bi-directional communication between the gut bacteria and the brain occurs through neural, immune, and endocrine pathways[12,48,139,140] which may be modulated by sex hormones, in particular estrogens. In fact, it has been recently reported that the microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner[141]. Clarke *et al*[141] found that male germ free mice, unlike females, display a significant elevation in the hippocampal concentration of 5-HT and its metabolite, compared with conventionally colonized control animals.

Numerous studies have reported the effects of sex hormones on the dimorphic sex differences in the response to microbial and viral infections[132]. Besides the role of sex hormones in the modulation of the immune system, they have a direct effect over bacterial metabolism, growth, and expression of virulence factors. For instance during pregnancy, the proportion of certain bacteria species associated with plaque microbiota is altered with a noticeable increase in the ratio of anaerobic to facultative bacteria[142]. Of significance, recent studies indicate that steroid nuclear receptor expression including ER-β can determine the intestinal microbiota composition[143].

Moreover, the gut microbiota may also affect estrogens metabolisms and their systemic level[144]. Conjugated estrogens are excreted in the bile and pass into the distal ileum, where they are variably deconjugated and may be reabsorbed from the gut lumen and enter the circulation *via* the portal vein[145]. It has been shown in men and postmenopausal women that the intestinal microbiota richness and function, associated for example with β-glucuronidase activity, influence levels of non-ovarian estrogens *via* enterohepatic circulation[146]. Bacteria are capable of metabolizing sex hormones through the activity of various enzymes such as hydroxysteroid dehydrogenase that regulate the balance between active and inactive steroids[130]. In particular, fecal bacteria can perform hydrolytic, reductive and oxidative reactions of estrogens and androgens[147]. Reversible 17β reduction of androgens carried out by the gut microbiota is suggested to play a role in the regulation of testosterone level[148]. The results of a landmark study published recently by Markle *et al*[149] provide astonishing conclusions indicating that sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. In the study performed in the non-obese diabetic mouse model of type 1 diabetes, they showed that male puberty in mice leads to changes in the gut microbiota that reinforce testosterone production, which is protective against the development of T and B cell functions linked to autoimmune disease[149]. In mice, the properties of the male-associated microbiota can be transferred to younger females and exert testosterone-mediated protection from autoimmune disease upon recipients. The observations that early-life microbial exposures determine sex hormone levels and modify sex-mediated immune regulation may have crucial implications for the pathophysiology of IBS. A new concept of "microgenderome" is emerging based on the recent observations that the gender bias present in numerous diseases is not entirely a host-intrinsic factor, but may be exercised and/or reinforced by the commensal microbiota of the host[150]. Undoubtedly, further studies are needed to elucidate the role of microgenderome in IBS.

THERAPEUTIC IMPLICATIONS

The modulator role of sex hormones on the bi-directional interactions within the brain-gut-microbiota axis may have significant therapeutic implications in IBS. However, although gender differences in responses to treatment modalities exist, the approach to IBS patients in both genders is quite similar so far. Clinical observations confirm that alosetron, a 5-HT_3 receptor antagonist, is more effective in improving urgency and loose stools in IBS-diarrhea predominant women than men[120,151,152]. The basis for this noticeable sex difference in therapeutic efficacy of alosetron could be associated with sex-related differences in 5-HT_3 receptor expression, lower alosetron clearance in women, and/or greater 5-HT synthesis in certain brain regions in IBS male patients compared with female IBS patients[153]. Sex difference in genetic polymorphism of the 5-HT transporter (SERT) promoter region has been also suggested and may induce the different expression of affective symptoms in women compared with men[154]. Additionally, the potential role of interaction between gonadal hormones and the cytochrome P450 pathway may be considered in sex-related differences in drug clearance[155]. Differences in adipose tissue compartment in women compared to men may affect this process as well[40].

Women with IBS are more susceptible to anxiety and depression and other stress-related disorders. However, in the study comparing the efficacy of treatment with paroxetine alone or combined with psychotherapy, no gender effect was reported[156]. Preliminary observations suggesting that IBS female patients may better respond to hypnotherapy[157] is yet to be confirmed. The recent results of randomized controlled trial have shown that gender, age, disease duration and IBS type have no influence on the long-term success of gut-directed hypnotherapy[158].

Regarding the role of sex hormones in the pathogenesis of IBS, therapeutic approaches aiming to suppress ovarian steroidogenesis have been also considered. In fact, gonadotropin-releasing hormone agonist (leuprolide)

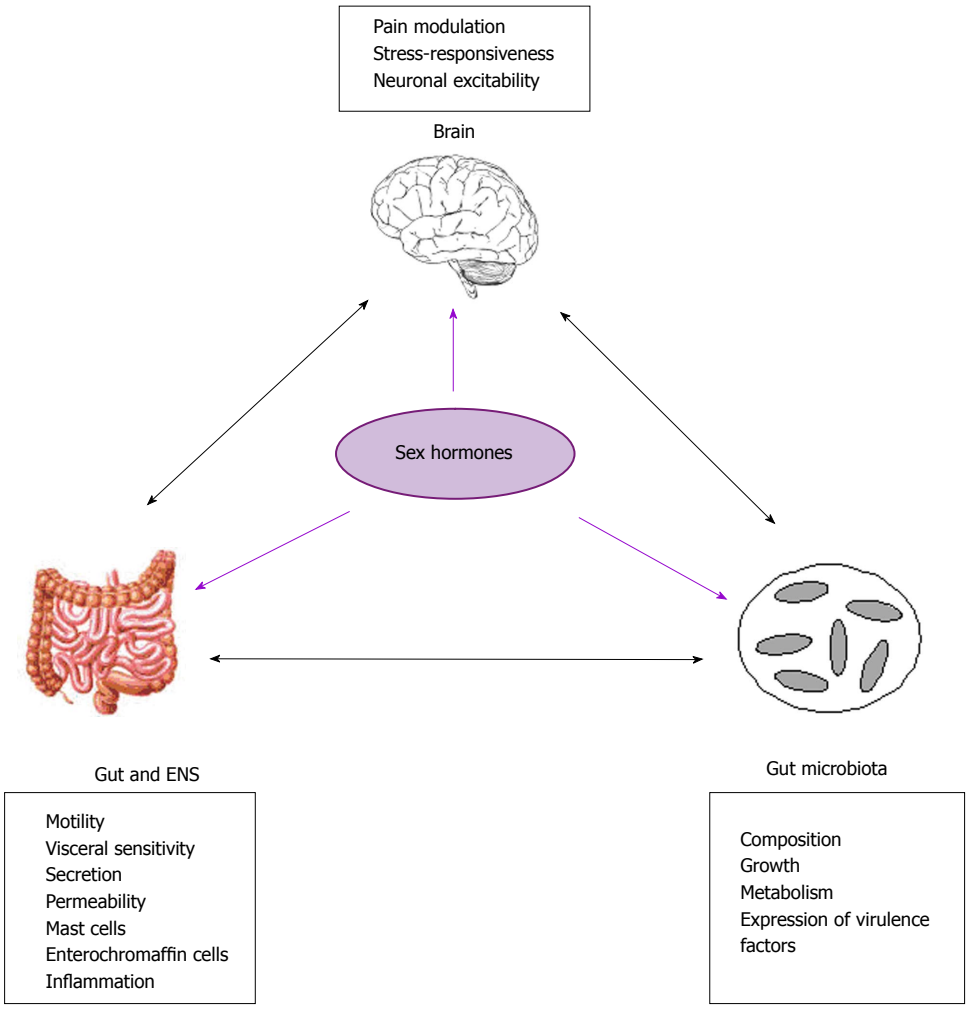

Figure 1 Sex hormones in the mutual brain-gut-microbiota interactions. Sex hormones influence peripheral and central regulatory mechanisms involved in the pathophysiology of irritable bowel syndrome contributing to the alterations in stress response, visceral sensitivity and motility, intestinal barrier function, and immune activation of intestinal mucosa. Sex hormones have also a direct effect on the gut microbiota. ENS: Enteric nervous system.

was reported to be effective in IBS female patients with menstrual cycle-related symptoms[57]. Nevertheless, many unpleasant side effects of leuprolide similar to climacteric-like syndrome significantly limit its application[57].

Noteworthy, interactions between gonadal hormones and pain modulation are bi-directional, as pain therapies in different experimental and clinical conditions have been found to affect the gonads as well[159,160]. For example, morphine treatment increased estrogen receptor, androgen receptor and *TRPV1* genes expression in the ovary, whereas in the testis the opiate reduced ER-α and ER-β mRNA expression not affecting androgen receptor and *TRPV1* expression[160].

A pivotal interdependence between the composition and stability of the gut microbiota and GI function as well as stress-related behavioral changes indicate a great therapeutic potential of probiotics, prebiotics and antibiotics in IBS[161,162]. So far, no gender specificity in probiotics efficacy in IBS patients has been reported[163]. Nevertheless, in the light of the microgenderome concept and sex-dependent differences in the immune regulation driven by gut microbiome[150], gender specificity in microflora manipulation seem to be essential and is expected to be extensively explored in the near future.

CONCLUSION

The results of epidemiological studies and clinical observations confirm significant sex and gender differences in the IBS prevalence and symptomatology. Furthermore, a growing number of clinical and experimental data strongly support a crucial role of sex hormones in the regulatory mechanisms of the brain-gut-microbiota axis involved in the pathophysiology of IBS (Figure 1). Some discrepancies in the results, especially related to the influence of estrogens, may result from different experimental conditions or heterogeneous groups of patients (*e.g.*, different age, menstrual status), but they also reflect the very complex nature of sex hormone actions. Estrogens can induce dual effects, both analgesic or hyperalgesic, as well as pro- or anti-inflammatory. Noteworthy, alterations in estrogen-induced visceral sensitivity seem to depend not only on the gonadal hormones levels, but more so on sudden changes in their levels, their sus-

tained genomic effects, and complex interactions with other neurotransmitters. Concomitant alterations in the number (up- or down-regulation) and sensitivity of ERs may play a crucial role in these processes as well. Thus, the physiological fluctuation in sex hormones may evoke for example different responses in IBS female patients compared to healthy women. Furthermore, a growing body of evidence indicates a protective role of androgens in pain modulation and anti-inflammatory properties of testosterone that may inhibit the development of visceral hyperalgesia. That could contribute to the higher susceptibility of women to IBS. A better understanding of the role of sex hormones in the modulation of the brain-gut-microbiota axis should enable a more effective and sex-tailored therapeutic approach in IBS.

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