Published in final edited form as:
Gastroenterol Pol. 2010 ; 17(2): 89–97.

Sex difference in irritable bowel syndrome: do gonadal hormones play a role?

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Abstract

Sex and gender effects in irritable bowel syndrome (IBS) have been reported in epidemiological, physiological, and clinical treatment studies. The potential role of gonadal hormones is discussed based on the female predominance in IBS and the correlation between IBS symptoms and hormonal status. Several different models have been proposed to examine the role of sex hormones in gastrointestinal (GI) function, including changes in GI symptoms during the menstrual cycle and differences in symptom expression in pre- and post-menopausal women as well as changes during pregnancy, hormonal treatment, or after ovariectomy. Gonadal hormones, in particular estrogens, can significantly modulate various clinical manifestations of IBS, including alterations in GI motility and visceral hypersensitivity. Additionally, sex differences in the stress response of the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system are considered to be contributing factors in the pathogenesis of functional bowel disorders. The modulatory effects of estrogens on visceral pain may result from interactions with numerous neurotransmitters at different levels of the brain-gut axis, with a pivotal role of estrogens' interactions with the serotonin and corticotropin-releasing factor (CRF) signaling systems. Estrogens can also modulate neuroimmune interactions triggered by stress via the brain-gut axis. Sex differences in the biological actions, pharmacokinetics, and treatment efficacy of serotonergic medications clearly suggest sex differences in pain pathways that have to be taken into consideration in therapeutic interventions.

Keywords

gonadal hormones; menstrual cycle; pain sensitivity; irritable bowel syndrome

The role of gonadal hormones, as potent and omnipresent steroid hormones, is being increasingly recognized in the physiology and pathology of the gastrointestinal (GI) tract (1). In experimental studies, gonadal hormones have been shown to affect both the motor

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and sensory function of the GI tract (2). Irritable bowel syndrome (IBS) is a gastrointestinal sensory and motility disorder characterized by abdominal pain or discomfort associated with a change in bowel habits (3). The potential role of sex hormones in gender differences regarding the epidemiology, pathophysiology, and treatment outcome in IBS patients has been proposed based on the female predominance as well as the correlation between IBS symptoms and hormonal status (menstrual cycle phases, pregnancy, menopause, hormonal replacement therapy) (4).

In the present article we will review the clinical findings assessing hormonal status and IBS manifestations as well as clinical and experimental evidence that gonadal hormones influence peripheral and central regulatory mechanisms of the brain-gut axis and stress-induced disease susceptibility at the levels of stress perception, stress physiology, and recovery. It is worth noting that the terms “sex” and “gender”, while related, are not interchangeable. Sex refers to biological distinctions characterizing male and female, whereas gender reflects sex-related social roles with which an individual identifies and that presumably reflect learned femininity or masculinity (5).

Sex and gender differences in IBS prevalence

In Western countries the prevalence of IBS in women outnumbers that in men by approximately 2:1 (6). While the ratio of female to male IBS sufferers in the non-patient population is 2:1, within the patient population who seek consultation with primary care physicians, females outnumber male patients by 3:1 (7). In tertiary care settings, the number of female IBS patients is even 4 to 5 times higher than the number of males (6,8). The prevalence rate should not be attributed only to sex strictly speaking, but also to gender-related differences in healthcare-seeking behavior and sociocultural characteristics that vary between men and women with IBS as well as among different cultures (6). For example, the female predominance in IBS has not been observed in a number of Asian countries, such as India, China, and Korea (9).

Sex-related IBS prevalence appears to emerge around the time of puberty and increases during the early adult years. Among women, the age at which IBS occurs most commonly is the late teens to mid-forties, which additionally suggests the role of reproductive hormones in the pathophysiology of the disease. With increasing age, the incidence of IBS in women decreases and approaches the rate among men around the age of 70 years old and above (10). The prevalence of IBS among men is fairly constant within the age range of 20–70 years (10). Additionally, the prevalence of many other chronic pain disorders frequently overlapping with IBS, such as fibromyalgia, migraine headache, chronic pelvic pain, and chronic fatigue syndrome, are is characterized by a female predominance and correlation between their symptoms and hormonal status has been reported (11–13).

Correlation between IBS symptoms and fluctuations in gonadal hormones

Women with IBS are more likely to report constipation, bloating, severe abdominal pain, and the feeling of incomplete evacuation than men with IBS (14). Men with IBS generally have diarrhea more frequently than women with IBS. Higher levels of somatic complaints and greater sleep disturbances are reported by women than men regarding IBS patients (15).

Women with IBS more frequently show co-morbidity with affective or mood symptoms, including anxiety and depression, than women without IBS (16). However, up to now there has been a lack of adequate data assessing sex- and gender-related differences in the psychological symptomatology of female and male IBS patients, although a recent report indicates that women with IBS exhibit more anxiety and depressive symptoms than men (15).

Menstrual cycle

The menstrual cycle is governed by tightly orchestrated changes in the levels of ovarian hormones and is commonly divided into three phases: the follicular (proliferative) phase, ovulation, and the luteal (secretory) phase. Estrogen levels rise and fall twice during the menstrual cycle. Estrogen levels increase during the mid-follicular phase and then drop precipitously after ovulation. This is followed by a secondary rise in estrogen levels during the mid-luteal phase, with a decrease before menstruation. The secondary rise in estradiol parallels the rise in serum progesterone and 17-hydroxyprogesterone levels (17). Dynamic changes in ovarian hormones during the 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 regulating these functions (3). The severity of GI symptoms, including abdominal pain or discomfort, altered bowel habits, and bloating, varies across the menstrual cycle phases (18–21). Therefore the menstrual cycle provides a natural model to explore the effects of ovarian hormones on bowel function.

Clinical studies indicate that declining or low ovarian hormone levels in women (such as during menses) may contribute to the occurrence or exacerbation of bowel symptoms. Approximately one third of otherwise asymptomatic women experience GI symptoms at the time of menstruation (19). Chang et al. also found that about 40% of women with IBS reported an influence of the menstrual cycle on their symptoms (20). In another study, bloating was shown to worsen premenstrually in up to two thirds of women with IBS (21). Whitehead et al. 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 ovarian hormones (18). The variation in GI symptoms during the menstrual cycle can be related to motor disturbances and/or a change in perception of colonic motor events (22). Rectal sensitivity thresholds have been shown to be significantly lower in IBS patients at menses compared with other cycle phases, indicating that the IBS symptom perceptionmay be modified by ovarian hormone status (tab. I) (23).

Menstrual disturbances such as primary dysmenorrhea (painful menstruation) frequently overlap with IBS and may be considered as a coexisting menstrual-linked syndrome. IBS patients with dysmenorrhea report noticeably more GI symptoms than non-dysmenorrheic women (24). In addition, women with IBS are more likely to report dysmenorrhea and premenstrual distress syndrome than those who do not suffer from IBS (25). Oral contraceptives often reduce symptoms in women with dysmennorhea, but their impact on IBS symptoms is less clear (8). Some association between IBS and endometriosis has also been reported (26). Additionally, polycystic ovary syndrome (PCOS), the most common

female endocrine disorder affecting up to 10% of reproductive-age women, has been shown to be associated with the increased prevalence of IBS (27). When IBS coexisted with PCOS, higher BMI and percent body fat were seen compared with PCOS alone (27). The relationships between obesity, hormonal status, and IBS require further investigation, particularly in the context of obesity being linked with increased inflammatory mediators (28). Other potential mechanisms of overlap between IBS and chronic pelvic pain disorders such as interstitial cystitis may include neural cross-talk via the convergence of pelvic afferents and visceral cross-sensitization. Experimental studies indicate that acute colitis sensitizes urinary bladder afferents to both mechanical and chemical stimuli and that chronic colitis similarly produces neurogenic cystitis (29).

Oral contraceptives

The natural decline in progesterone and estrogen levels during the late luteal phase is suggested to result in the increase in abdominal pain/discomfort at premenses and menses. Healthy women taking oral contraceptives (OCs), either monophasic or triphasic preparations, show a typical increase in GI symptoms at menses. However, women with IBS who were taking OCs containing both estrogen and progestin appeared to have reduced levels of abdominal symptoms compared with IBS women who were not taking OCs (30). Nevertheless, the pattern of GI and non-GI symptoms over the menstrual cycle was generally similar in female IBS patients, regardless of OCs use or the predominant bowel pattern (30).

Pregnancy

During pregnancy, ovarian hormone levels as well as opioid-mediated antinociception are elevated (3). Many chronic pain syndromes frequently associated with IBS, such as migraine headaches, are alleviated during pregnancy (11). During the time of physiological hyperestrogenemia and hyperprogesteronemia, prolonged GI transit is observed (31). Constipation is one of the most common complaints of pregnant women. However, apart from high ovarian steroid levels, the direct effect of a growing fetus on bowel function should be considered. Additionally, psychological distress affecting the autonomic nervous system (ANS) may trigger or modulate symptoms reported in pregnant women (32). In rodents, high ovarian hormones levels during pregnancy reduce somatic and visceral pain sensitivity (33).

Menopause

Whether the decrease in IBS incidence associated with age in women is linked to the decline in ovarian hormone levels is not clearly established. Data on the impact of the menopause transition on IBS patients are inconsistent. The decline in ovarian hormones may induce or exacerbate GI symptoms; however, during the postmenopausal period, the incidence of IBS generally decreases significantly (34, 35).

Cain et al. reported that in postmenopausal women with IBS, higher levels of GI pain-related symptoms, including abdominal distension and bloating, compared with men are observed (15). However, when controlled for age, the differences in GI symptoms of discomfort were no longer significant. Additionally, postmenopausal women reported higher

levels of somatic discomfort symptoms (muscle and joint pain) than men and menstruating women and these differences persisted after controlling for age. There was also no significant difference in psychological distress indicators, such as anxiety and depression, among the three groups (15).

Hormonal replacement therapy

Hormonal replacement therapy (HRT) has been reported to be associated with the increased prevalence of IBS in postmenopausal women. HRT may prolong IBS symptoms to a later age or even induce changes in GI function in women not affected previously (36). It should be taken into account that women with IBS may be more likely to report various pre- and postmenopausal symptoms and thus may be prescribed HRT to a greater degree (4). However, Ruigomez et al. showed that both current and past users of HRT presented an increased risk of IBS compared with non-users, even after adjusting for comorbidity and consultation pattern (36). This increased risk was irrespective of treatment duration, regimen, or route of administration of HRT (36).

Gynecological surgery

There are few data concerning the prevalence of ovariectomy or hysterectomy in female IBS patients. To some extent this may result from the fact that women who have undergone these surgical procedures may be excluded from studies of patients with IBS. However, it has been reported that the rate of hysterectomy is about twice as high in women with IBS than in healthy controls (37). One explanation could be 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 such as cholecystectomy and appendectomy) (37). Whether ovariectomy itself might be a risk factor for developing IBS is unknown. However, in a number of women, GI symptoms emerge for the first time after gynecological surgery (38). In contrast, an animal model, it was shown that ovariectomy abolished stress-related visceral hypersensitivity induced by colorectal distension (39). Conversely, estrogen replacement in ovariectomized rats at a dose comparable to the proestrus level restored visceral hypersensitivity to colorectal distension and enhanced the effect of intraperitoneal corticotropin-releasing factor (CRF) injection through CRF, receptor interactions, resulting in increased defecation and watery diarrhea (40).

The male connection

While most of the explanations of sex-related differences in IBS have focused on the concept that women might be more susceptible, little attention has been given to the possibility that male hormones may be protective against pain disorders (41). 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 (42). Differences in androgen levels, receptors, as well as sites of action may play a role in the sex difference and the risk of developing chronic pain disorders. Increased levels of androgens, in particular testosterone, appear to decrease pain in both men and women (43).

However, there are only a few reports concerning the role of sex hormones in men with IBS (41, 44, 45). A recent study found that middle-aged men with IBS tended to have lower

levels of luteinizing hormone (LH) than healthy men (41). A tendency for IBS symptomatology to be inversely related to testosterone levels has been shown (41). Kim et al. also reported that the sex hormone status of young male patients is different from that of older male patients and that an elevated sex hormone-binding globulin (SHBG) level might play a key role in the pathophysiology of IBS in young men (44). Interestingly, a highly significant reduction in male-trait scores in men with IBS has been confirmed (45).

Transsexual individuals

Aloisi et al. proposed a unique model to study the relationship between sex hormones and the occurrence and incidence of chronic pain in transsexual women and men who undergo a drastic change in their hormonal status as healthy adults (46). Cross-sex hormone administration not only has the expected sex-specific effects on the somatic characteristics of the subjects, but also changes the occurrence of pain. About one third of the male-to-female subjects developed chronic pain, including headaches, breast and musculoskeletal pain, and in some cases visceral pain as well, concomitantly with estrogen/anti-androgen treatment. Conversely, about half of the female-to-male subjects treated with testosterone reported a significant improvement in chronic pain (mainly headache) present before the start of the treatment (46). These findings support experimental and clinical data suggesting that sex steroid hormones play a crucial role in pain perception and modulation.

Action of gonadal hormones at different levels of the brain-gut axis

There is compelling evidence that gonadal hormones, in particular estrogens, can significantly modulate various manifestations of IBS, including alterations in GI motility, secretion, visceral hypersensitivity, serotonergic system regulation, ANS disturbances, and stress responsiveness (6,47,48).

Estrogen receptor expression

The response to estrogens is tissue specific and may depend on the specific estrogen receptor (ER) subtypes belonging to the family of nuclear receptors. Besides the rather slow onset and long-lasting genomic action of estradiol mediated by the classical nuclear ERs, there are also rapid effects frequently associated with ERs located on the plasma membrane, where ligand-ER interactions trigger the activation of various protein-kinase cascades (49). There are two types of ERs identified: ER-α and ER-β. ERs located in the cytoplasm are translocated to the nucleus after ligand binding. ER activation results in enhancement or repression of gene transcription and thus protein synthesis alterations (49). In addition, a membrane-located G protein-coupled receptor, GPR30 (an alternative to the classical ERs), has recently been identified to be involved in the rapid action of estrogens through G protein signaling and related phosphorylation of many proteins. The abundant distribution of both ERs at all levels of the brain-gut axis, including the central nervous system (CNS), spinal cord, and enteric nervous system, supports a multiplicity of neuronal actions, including the activation of excitatory glutamate receptors (48). The co-expression of ERs in enteric neurons indicates that estrogenic effects could also be mediated through neurogenic reflexes (48). ERs, in particular ER-β, are also located on epithelial cells throughout the GI mucosa and may affect secretory and absorptive function (18, 50). In particular, the extra-nuclear

action of estrogen can stimulate calcium entry into colonic epithelial cells as well as suppress c-AMP-dependent chloride secretion in the distal colonic epithelium in rats and humans. This has only been observed in females, not males, and contributes to the fluid retention that occurs in females during the cycle (51).

Estrogen/progesterone in pain modulation

While estrogens are commonly known as a CNS stimulant, androgen receptor-mediated actions are often related to CNS inhibition, which has been suggested to explain the lower incidence of many forms of chronic pain in men (46). Estrogens have been documented to exert differential, sometime opposite, effects on pain. In particular, human and experimental animal models indicate that both analgesic and hyperalgesic responses can be induced by estrogens depending upon the experimental conditions (42). These effects can be mediated by the receptor modulation that occurs with hormonal changes (e.g. upregulation of receptors in peripheral tissue). A rapid increase in estrogen levels is associated with alterations in excitability of nerve fibers and brain cells, including those that may contribute to pain sensation (43). Estrogens modulate the responsiveness of primary afferent neurons to substance P and the activation of glutamate receptors involved in afferent pain pathways (22). Recently, experimental studies showed that ovarian steroids can modify the stress-related activity of colonic tachykinin NK1 receptors, thus affecting pain transduction (39). Elevated levels of estrogens in fertile women have been associated with increased number of μ-opioid receptors, which are activated by endogenous pain-relieving neurotransmitters such as endorphins and enkephalins, in regions of the brain related to pain processing (43).

The role of progesterone in sex-related differences in pain sensation is less clear. Laboratory studies have shown that gonadal hormones such as progesterone, luteinizing hormone, human chorionic gonadotropin, and relaxin (but not estrogen) inhibit GI motility (52). Progesterone acts on intracellular receptors to regulate genomic processes and also affects cell membrane receptors, especially neuronal receptors (52). The action of progesterone seems to be dependent on the activation of γ-aminobutyric acid (GABA) receptors, major inhibitory receptors in the brain (50). Progesterone has also been suggested to influence both visceral sensitivity and motility via prostaglandins (13). In women with slow transit constipation, over-expression of progesterone receptors in colonic muscle has been shown to be associated with lower levels of prostaglandins (PGs) that cause muscle contraction ($PGF_{2\alpha}$ and tromboxane A) and higher levels of PGs that cause muscle relaxation (such as PGE_2) (53).

Recently, based on brain imaging studies, it was suggested that in addition to the multiple peripheral and spinal mechanisms proposed for sex differences in visceral pain sensitivity, modulation takes place predominantly in the brain (54). ERs are spread throughout the brain, including the hypothalamus, pituitary, hippocampus, cerebral cortex, mid-brain, and brain stem, indicating a great potential for numerous influences of estrogens on neurocognitive processes (48). Estrogens may act in the CNS through multiple pathways modulating neurotransmitter production and action, influencing electrical excitability and synaptic function, and changing the morphological features of neural elements involved in the function. There is accumulating and convincing evidence that estrogens have a significant

impact on the neuronal plasticity-related process and ameliorate recovery after chronic stress (tab. II) (48). Recent findings from functional magnetic resonance imaging have shown that sex differences in brain activity in the stress response circuitry are dependent on women's menstrual cycle phase (55).

Additionally, alterations in the number of ERs at different levels of the brain-gut axis, correlated with the fluctuation of ovarian hormones through the menstrual cycle, can affect visceral nociception. In female rats, estrogens have been shown to enhance visceral signaling following colonic inflammation, whereas progesterone seemed to counteract the effect of estrogens on colorectal sensitivity (56).

Serotonin-estrogen interactions

The serotonergic system represents another potential contribution to sex differences in the modulation of GI motility, secretion, and sensitivity (3, 57). Fluctuations in estrogen levels during the ovarian cycle cause predictable changes in the serotonin (5-HT) system in women (57). It has also been shown that the 5-HT concentration varies with gender and menstrual status in patients with diarrhea predominant IBS (IBS-D) (58). In the CNS, 5-HT has generally been associated with descending pain inhibition, whereas peripheral 5-HT is an inflammatory mediator and is generally pronociceptive and prokinetic. The serotonergic system and the (CRF) system regulating stress response are both known to be modulated by estrogens (e.g. estrogens enhance serotonergic postsynaptic responsiveness in the brain) (57). The serotonergic and reproductive endocrine systems are also both prominently involved in the regulation of mood and behavioral states, and interactions between these systems have significant implications for the etiology and treatment of anxiety disorders (59).

Clinical observations confirm sex-related differences in 5-HT_3 receptor antagonist efficacy in the treatment of IBS (60). It has been hypothesized that some of the modulatory effects attributed to estrogens may be a consequence of estrogen-related changes in serotonin efficacy and receptor distribution. In particular, 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 (61).

Autonomic nervous system dysregulation

Male versus female differences in bowel function may also be related to differences in the ANS, which provides the major link between the brain and the gut. Tillisch et al. reported gender differences in ANS reactivity to colorectal distension in IBS patients, with men demonstrating increased sympathetic nervous system activation and decreased parasympathetic activation compared with women (62). Sex-related differences in basal ANS tone can be correlated with stress arousal and reactivity as well as the interpretation of stressful stimuli. The sex differences in autonomic function among IBS patients are likely to results from estrogen exposure, which attenuates sympathetic responsiveness (62). Much less is known about the effects of progesterone and testosterone on the ANS.

Gender differences in ANS function markers, such as heart rate variability, relating to gonadal hormones cannot be ascertained, although there are some data indicating that there are menstrual cycle-linked differences in ANS tone particularly in symptomatic women with IBS (63). It has been proposed that many other chronic pain syndromes frequently coexisting with IBS can also be related to ANS disturbances (12).

Sex differences in stress response

The sex difference in the physiological response to stress has recently emerged as a potentially important factor in the pathophysiology of functional gastrointestinal disorders (6, 8, 22). Stress and anxiety can not only trigger IBS symptoms, but also have impact on their severity. A number of clinical and experimental studies have documented sex differences in the regulation of the stress response and the hypothalamic-pituitary-adrenal (HPA) axis indicating of the role of sex hormones in these processes (64). Menstrual cycle phases, menopausal status, and pregnancy have been shown to affect the HPA axis and ANS functions significantly (5). Women between puberty and menopause usually show lower HPA-axis and autonomic responses to psychological stressors than men of the same age (65). However, the HPA axis response to a psychological stressor is higher in the luteal phase when, for example, the post-stress free cortisol level approaches that of men.

The activation of CRF signaling pathways has become an established key effector in the endocrine, behavioral (anxiogenic), and visceral limb of the stress response (66). CRF also affects GI physiological functions via both central and peripheral interactions with CRF receptors and appears to play an important role in the brain-gut response to stress (67). Interestingly, CRF can be modulated by estrogens at the molecular level. Recently, both receptors, ER-α and ER-β, have been shown to stimulate CRF gene expression, providing another link in the cross-talk between estrogens and the HPA axis (64). Additionally, recent studies have established that chronic treatment with estrogens modulates brain circuitry responsive to stress (68). Co-localization of ER-α and CRF in the hypothalamus is one of the possible neuroendocrine interactions between CRF signaling pathways and ERs (69). Variation in the hormonal status can affect the colonic motor response to stress. Preliminary data indicated an interaction between CRF-CRF_1 receptor pathways and estrogens in the stimulation of colonic motor function that may take place within the enteric neurons of the colon, where both CRF_1 and ERs are expressed (68).

Neuroimmune interactions

Complex interactions between the HPA axis, the immune system, and the reproductive system have been postulated in which estrogens and CRF may play a pivotal role. Activation of CRF signaling not only coordinates the stress-related alterations of gastrointestinal motility and sensitivity, but also neuroimmune mechanisms of the intestinal response to stress (66, 70). The complex nature of these multidirectional neuro-endocrine-immune interactions is connected with the fact that some peptides (such as CRF) and some cytokines (such as interleukin 1-β) mediate both stress and inflammatory responses (71). A local paracrine/autocrine proinflammatory 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 expression in immune cells of the human colonic lamina propria in response to inflammation (67). There is compelling evidence suggesting an up-regulated gut immune function in patients with IBS, particularly with post-infectious IBS (72). Intestinal inflammation seems to be strongly modulated by stress, especially in IBS patients characterized by enhanced stress responsiveness (8). Important sex-related differences in IBS patients related to neuroimmune interactions have been suggested (45). Female sex is an independent risk factor for developing post-infectious IBS (3). Estrogens may influence both pro- and anti-inflammatory pathways. The effect of estrogens in inflammatory responses has been found to be extremely complex and dependent on estrogen level, cell type, specific inflammatory factors, the type of inflamed tissue, the time course of the inflammatory response (e.g. acute vs. chronic), and the time point at which estrogen exposure occurs (73).

Interestingly, gender-related differences in low-grade intestinal inflammation in IBS patients have been established. The number of colonic mucosal mast cells was found to be higher in female than in male IBS patients (74). Mediators released by activated mast cells, characterized by extensive anatomical and functional communication with the intrinsic and extrinsic nervous systems of the gut, evoke visceral hypersensitivity and increase mucosal permeability (75). Notably, mast cells have been 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 are reduced during pregnancy (12, 29, 74). 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 (74). Estradiol has been shown to augment mast cell secretion, whereas tamoxifen, an estradiol receptor antagonist, inhibits this function (76). Activation of progesterone receptors inhibits mast cell degranulation (77). The link is between the low levels of both estrogen and progesterone at the time of menses when exacerbation of IBS symptoms is observed remains unclear.

Therapeutic implications

Clinical trials with a 5-HT_3 receptor antagonist (alosetron) revealed a noticeable sex difference in therapeutic efficacy, suggesting a conceivable link between 5-HT_3 receptors and ovarian hormones (60, 61). The reasons to explain these observations include 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 male compared with female IBS patients (78). Genetic polymorphism of the 5-HT-transporter (SERT) promoter region has also been suggested to be associated with the different expression of affective symptoms in women compared with men (79). The potential role of the interaction between gonadal hormones and the cytochrome P450 pathway may also be considered in sex-related differences in drug clearance. The substrates of cytochrome P450 enzymes include metabolic intermediates such as lipids and steroid hormones as well as xenobiotic substances such as drugs. Moreover, a different adipose tissue compartment in women compared with men may affect drug distribution and clearance.

In view of the potential role of gonadal hormones in the pathogenesis of IBS, therapeutic approaches aimed to suppress ovarian steroidogenesis have been considered. In fact, the

effectiveness of gonadotropin-releasing hormone agonist (leuprolide acetate) administration to female IBS patients with menstrual cycle-related symptoms has already been reported (80). The therapeutic efficacy of leuprolide inducing a hypoestrogenic state in women with menstrual cycle-related IBS symptomes might be explained by the reduction of the effect of ovarian hormones on bowel function in females highly susceptible to sex hormones. Nevertheless, its indirect action on mood and thus on bowel symptoms should also be considered (80). However, due to the unpleasant side effects of leuprolide, consisting of climacteric-like syndrome, the treatment should be considered for a highly selected population only (80).

Summary

Clinical and experimental data strongly indicate an important role of gonadal hormones in the regulatory mechanisms of the brain-gut axis involved in the pathophysiology of IBS (tab. II). However, many of the results, especially for estrogens, appear to be inconsistent or even contradictory. This may result in part from different experimental conditions or heterogeneous groups of patients (e.g. different age, menstrual status); however, it primarily reflects the very complex nature of actions and interactions of the gonadal hormones at the different levels of the brain-gut axis. Estrogens can induce dual effects, both analgesic and hyperalgesic, pro- and anti-inflammatory. Noteworthy, alterations in estrogen-induced visceral sensitivity seem to be related not only to the basal level of gonadal hormones, but more so to sudden changes in their levels as well as receptor modulation processes (up- or down-regulation) and complex interactions with other neurotransmitters. The physiological fluctuation in the ovarian hormones may evoke different responses in female IBS patients than in healthy women. Altered susceptibility to sex hormones in IBS can explain some confusing observations regarding estrogen actions. The sudden decline in estrogen levels observed in premenstrual phase usually exacerbates IBS symptoms, whereas the generally lower estrogen levels in postmenopausal women seem to be associated with alleviation of these symptoms (tab. I). Concomitant alterations in the number and sensitivity of estrogen receptors may play a crucial role in these processes. Recognizing the influence of sex-linked biology on IBS remains a critical component in developing an effective therapeutic approach.

Acknowledgments

The authors are grateful to Dr. Lin Chang, MD, for her critical comments on the manuscript and wish to thank Miss Eugenia Hu for her editorial assistance.

This work was supported by a VA Research Career Scientist Award and the National Institute of Diabetes and Digestive and Kidney Diseases Grant, P50 DK-64539 (YT) and the Kosciuszko Foundation (AM).

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TABLE I

Correlation between hormonal status and IBS symptom expression

Status	Hormone levels	IBS and pain-related symptom expression	Reference
Late luteal phase (premenses)	rapid decline in estrogen and progesterone levels	exacerbation of bowel symptoms, increased bloating	17,19,21
Menstruation (menses)	lowest levels of estrogen and progesterone	exacerbation of bowel symptoms, increased abdominal pain/discomfort, lower rectal sensitivity threshold	18-20, 2223
Dysmenorrhea	disturbances in hormonal interactions at different regulatory levels (lower progesterone level)	exacerbation of bowel symptoms	24
Oral contraceptives	estrogen and progestin administration	reduced abdominal symptoms at menses	30
Pregnancy	physiological hyperestrogenemia and hyperprogesteronemia	reduced pain sensitivity and alleviation of many chronic pain syndromes, exacerbation of constipation (prolonged gastrointestinal transit)	11,31,48
Menopause	decline in ovarian hormones	decrease in IBS incidence, high prevalence of constipation and somatic discomfort syndromes	15,34,35
Hormonal replacement therapy (HRT)	estrogen (and progesterone) supplementation	increased prevalence of IBS in postmenopausal women during HRT, prolongation of IBS symptoms to a later age	36
Ovariectomy	ovarian hormone deficiency	exacerbation or occurrence of gastrointestinal symptoms after gynecological surgery	38
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 with women with IBS)	41,44
Transsexual women (male-to-female subjects)	estrogen/anti-androgen treatment	development of chronic pain including visceral pain	46

TABLE II

Modulation of the brain-gut axis by ovarian hormones

Level of the brain-gut axis	Estrogen	Progesterone
Central nervous system	analgesic or hyperalgesic effect (42) excitatory action on neurons (46) estrogen-induced increase in the number of μ-opioid receptors (43) enhancement of serotonergic postsynaptic responsiveness in the brain (57) central interaction with CRF signaling pathways - modulation of stress responsiveness (68) influence on neuronal plasticity-related processes (48)	activation of the y-aminobutyric acid (GABA) receptors, major inhibitory receptors in the brain (50)
Autonomic nervous system	attenuation of sympathetic responsiveness (62)	reduced cholinergic responsiveness (5)
Enteric nervous system//immune system	expression of estrogen receptors in enteric neurons - regulation of neurogenic reflexes (48) enhancement of visceral signaling following colonic inflammation (56) augmentation of mast cell secretion (76) effects on both pro- and anti- inflammatory pathways (73) peripheral interaction with CRF signaling pathways - modulation of colonic motor and sensory responses to stress (68)	inhibitiont of gastrointestinal motility (52) inhibition of visceral signaling following colonic inflammation (56) inhibition of mast cell degranulation (77)

CRF - corticotropin-releasing factor