Title: Age, Gender and Women's Health and the Patient

Short title: Gender and the Patient

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Abbreviations: ANS: autonomic nervous system; EAL: early adverse life event; FGID: functional gastrointestinal disorders; fMRI: functional magnetic resonance imaging; GI: gastrointestinal; HRT: hormone replacement therapy; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; QoL: quality of life.

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INTRODUCTION

This review discusses the patient's perspective and biological basis for sex and gender differences in functional gastrointestinal (GI) disorders (FGIDs). Attention is given to the lived experience of irritable bowel syndrome (IBS) as well as the importance of patient interaction with the health care provider. In addition, the review highlights the current literature related to gender- and sex-based differences in visceral and somatic sensitivity, pain, motility, and the overlap of FGIDs, in particular IBS, with other chronic conditions.

THE PATIENTS PERSPECTIVE

The Patient Experience of FGIDs

"IBS is very frustrating: it dominates life style and daily activities mostly through its unpredictability. You must always plan for the 'what if' 'what if I eat more' 'what if toilet facilities are not available' 'what if I cannot break away'. It leaves you feeling 'dirty or unclean' and inhibits social mixing and sexual activity. IBS is frustrating. And that's the bottom line……" IBS study participant.

For patients with chronic symptoms the psychological and social ramifications of their illness are often more important than the physical impairment . Three overriding themes seem to dominate the experience of living with moderate to severe FGID: 1) a sense of frustration, 2) a sense of isolation and 3) search for niche in the health/sick role continuum/dissatisfaction with the medical system.[1-4] The effects of IBS on quality of life (QoL) are often underestimated. Patients with mild to moderate disease severity report that IBS restricts daily activities on average 73 days per year (20%); resulting in loss of work (13% of patients).[5]

There is often a disconnect between patients' and physicians' views of the IBS experience, regarding perceptions of etiology, severity, treatment approaches, and efficacy.[6-8] When 1,014 patients and 508 physicians used identical scales to rate IBS-related pain and discomfort, responses showed that physicians rated discomfort as significantly less severe than patients.[9] Conversely, 35% of more than a

1000 IBS patients in an international survey, reported their symptoms as 'severe'. In the same survey, to receive a treatment that would make them symptom free, patients would give up 25% of their remaining life (average 15 yrs) and 14% would risk a 1/1000 chance of death.[5] Many patients are reluctant to accept the "functional" diagnosis and many misconceptions, for example that anxiety, depression, and diet cause IBS, and fear that IBS leads to cancer.[7, 8] Such misconceptions are likely affecting clinical outcomes and health care utilization.

The Patient-Health Care Provider Encounter

"The biggest problem is that no one (in the medical field) treats the whole person. I feel more like I'm going to a drug dealer than someone that looks at the problem in its totality. As a result I have turned my attention to helping myself, and have had some degree of success. I wish doctors would listen to patients more when we talk about the symptoms and how they affect our daily lives" IBS study participant.

Only a small proportion (≈25%) of IBS sufferers consult physicians.[10] However, those who do, have high health care utilization.[11] The nature of patient-physician relationship is complex. Factors within and outside the health care system are constantly molding patient and physician behavior. Patients feel frustrated with unsatisfactory explanation of FGIDs which may be experienced as a denial of the legitimacy of their symptoms and perceive lack of empathy.[2] Conversely, physician frustration and dissatisfaction related to treating patients with FGIDs stem from a lack of understanding of the disease, limited treatment options, limited training in communication skills, increased workload, and the perception of personality characteristics of patients with IBS with psychiatric comorbidities.[12] Gastroenterologists perceive that patients with IBS require longer visits despite not being as sick as patients with other disorders that they manage[9] and can show gender bias.[13] Negative attitudes toward patients with IBS may form a barrier to objective patient assessment and effective physician-patient relationship building, and ultimately negatively impact clinical outcome.[14] Effective communication skills can be learned and practiced and, importantly, do not increase the encounter time. Rather, effective

communication skills make the process of assessment and diagnosis more efficient, improve clinical outcomes and increase physician job satisfaction.[15-17]

IBS can be challenging for both the physician and the patient. Patients must learn to self-manage a condition that can have a profound impact on everyday life. Health care providers can help by eliciting and addressing patient concerns, by offering a positive diagnosis and clear, understandable, and legitimizing explanations of the disorder, show empathy and enter into a meaningful partnership that helps individuals replace feelings of helplessness with means of empowerment.

GENDER

Sex refers to the biological makeup of the individual's reproductive anatomy while gender refers to an individual's lifestyle or personal identity. Often these terms are used interchangeably. In this section we use sex to describe what is known about biological differences between males and females and gender to refer to what is known about behavior between men and women.

The literature on gender and health has discussed the detrimental impact of adherence to some traditional feminine gender roles on women's health and wellbeing.[18] These include gender-related expectations, such as societal standards for attractiveness; social norms regarding women's caretaking role in relationships; and sanctions against anger expression by women. The messages women receive about gender-related expectations and the societal consequences of not measuring up to these expectations, can have health consequences.[19] There are several common gender role concerns among women with IBS including; shame and bodily functions; bloating and physical appearance; and pleasing others, assertion and anger.[19]

One central theme that women with IBS commonly report is feelings of shame associated with losing control of bodily functions. Women are taught that bodily functions are something to be kept private and secret. One important implication of such teachings is that bowel functioning becomes a source of shame and embarrassment more so than it does for men.

The finding that women often score higher on indices of bloating and constipation can also be discussed as a gender-related theme. Society's focus on how women look (eg, thinness as a necessary standard of attractiveness)[20] can lead women to experiencing bloating not only as a source of physical discomfort, but of psychological distress as well. The physical and psychological distress that women may experience with abdominal discomfort, coupled with the perception that their pain is being minimized or trivialized by health care professionals, may lead women to respond by becoming more hyper-vigilant to any sign of pain or discomfort.

Women as compared with men are socialized to please others, often at the expense of their own needs. Women who express anger, make demands, or question authority are often given the label "*hysteric*," have their complaints dismissed, or have their femininity called into question. Potential repercussions for women who express their own wants and needs are often sufficient to keep women silent. These social expectations of women can lead to the silencing of certain thoughts, feelings, and behaviors rather than jeopardize relationships that are in place.[21] A study that compared women with IBS patients with women with inflammatory bowel disease (IBD) found women with IBS score higher on measures of self-silencing than IBD patients.[21] In another, women reported shame in not living up to gender norm expectations for women in domains of relationships (taking care of others at the expense of their own needs), attractiveness (due to bloating) and lack of desire to engage in sex (due to IBS symptoms).[22] Men in this study focused more on IBS symptoms impacting their paid employment and sense of control. They also found that in interactions with health care providers, women risked being trivialized and men risked being overlooked because IBS may be labeled as a women's health concern.

Gender and Social Factors

It is important to acknowledge that health and illness occur within a larger social context. The meaning and expression of illness occur against a complex backdrop of a multitude of social determinants of health. The social determinants that have been investigated in FGIDs include: life stressors, history of

sexual, physical, and emotional abuse, early life experiences including gender role socialization, social support, and social factors as assessed by QoL scales.

There are limited studies to date that have assessed gender differences in life stress related to FGIDs.[23] While the data support a significant role for life stress in IBS, future studies will need to determine whether there are differences in the relationship between stress and FGIDs in women and men. While stress affects the gut in most people, patients with IBS appear to experience greater reactivity to a variety of stressors.

One form of social stress that has received attention in the study of FGIDs is sexual, physical or emotional abuse.[24] Table 1 shows the summary of studies fcused on gender differences in history of sexual, physical and emotional abuse.[24-28] However, most work in this area has included only women or a women-predominate sample. Because of conflicts in the literature, more research is needed to determine whether there are gender differences in history of abuse in FGIDs.

Studies have also investigated whether women and men with FGIDs differ on health-related QoL measures.[29] For example, in a study of referral center and primary care patients, Simren et al[30] found that women with IBS reported a lower QoL compared with men with IBS. Similar results were found in a Chinese outpatient population.[29] Dancey et al[31] found that men and women with IBS reported similar QoL scores as well as similar levels of symptom severity, perceived stigma, and illness intrusiveness. However, these authors also found gender differences in the relationship among these variables. For example, among women, IBS symptom severity exerted a significant impact on QoL, whilstfor men, the psychosocial impact of illness intrusiveness was greater in every domain except sexual relations. The authors suggest that these results have implications for how socialization shapes IBS-related gender differences.

GENDER AND EPIDEMIOLOGY

Most individuals with FGIDs do not seek healthcare and the decision to seek care introduces bias in research. This section will focus on population-based research which is used to fully evaluate the

epidemiology and clinical symptoms in these individuals. The proposal that FGIDs may be more prevalent in women stems from a variety of sources reviewed elsewhere: studies documenting a greater prevalence of FGIDs with other chronic pain conditions which are more common in women (fibromyalgia, chronic pelvic pain), studies proposing an effect of the menstrual cycle on symptom severity and studies suggesting that particular agents are more effective in women**.**

Functional Esophageal Disorders

Functional esophageal disorders are common.[32] Globus sensation and rumination syndrome are reported by about 1 in 10 of the population[32-35] and are more common in women. Men with globus tend to have greater levels of somatization and depression.[33] The prevalence estimates of functional chest pain, based on self-report, vary between 12.5 to 25%[32, 36] with an equal gender prevalence in the general population.[32] There is a higher female-to-male ratio in tertiary care referral centers[37] and women tend to use terms like "burning" and "frightening" more than men.[38] The challenge in research studies of functional esophageal disorders is identifying those individuals who predominantly have a functional esophageal disorder rather than gastroesophageal reflux disease, which is not associated with gender difference in rates or reflux symptoms.

Functional Gastroduodenal Disorders

Functional dyspepsia affects 15-20% of the general population[39] and does not vary with gender.[39-41] Being a women was a significant predictor of functional dyspepsia when compared with organic causes of dyspepsia.[42] Although females have physiological evidence of delayed gastric emptying there is little relationship between these measures and symptom severity or hormonal status.[43, 44] Adolescent girls are twice as likely to report aerophagia as adolescent boys.[45] The overall prevalence of functional vomiting is 2.3% and there is no association with gender.[46]

Functional Bowel Disorders

Female-to-male ratios of IBS vary widely geographically, from 3:1 in urbanized Western populations to 1:1 in Nigeria[47] (Figure 1 and Table 2[25, 29, 30, 32, 34-37, 39, 40, 45-75]), but overall the prevalence of IBS internationally is 67% higher in women than in men (odds ratio 1.67 confidence interval 1.53-1.82).[47]

In terms of symptom severity, among patients with mild symptoms (< 3 Manning criteria), 65% were women, rising to 80% in those with more severe symptoms (≥ 3 criteria).[25] Women have a more impaired QoL with IBS, with the somatic symptoms correlated to a gender-related increased prevalence of anxiety and depression. [25]

There is a greater women to men predominance in non-pain associated symptoms of constipation, bloating, and extra-intestinal manifestations.[48] Women are twice as likely as men to report bloating or abdominal distention.[66, 67] Abdominal pain scores for men and women with IBS are similar; however, men report more diarrhea and women report more constipation.[30, 48, 60, 65] In addition, women with IBS were more likely to report bloating and nausea as well as extra-intestinal symptoms compared to men.[48] There is an amplification of GI symptoms during the late luteal and early menses phases.[76]

The female-to-male ratio for constipation is elevated for both the "outlet" (poor pelvic muscle tone) type and the combined "IBS+outlet" type of functional constipation [77]. Women with functional constipation were two-times more likely to seek medical care compared to men.[61, 62, 78] As with most FGIDs, the prevalence of functional constipation and IBS-constipation is lower in Asian populations, but the female preponderance is similar to Western populations.[79]

Functional abdominal pain is much more common in children and adolescents than adults, and the rate of diagnosis is higher in girls than boys.[68]

Functional Disorders of the Biliary Tract and Pancreas

The prevalence of sphincter of Oddi dyskinesia is 0.8%, being four to five times more common in women.[32, 55]

Functional Anorectal Disorders

Prevalence rates of fecal incontinence vary from 2% to 11%,[64, 70]. Among nursing home residents, incontinence is more common in men,[71] in contrast to older people living at home.[69] There is no difference in gender in functional anorectal pain.[32] Pelvic floor failure is common and increases with age, being more common in women.[32]

GENDER AND OVERLAPPING FUNCTIONAL DISORDERS

Patients with FGIDs often report other physical and mental comorbidities, ie, 'extra-intestinal' conditions.[80] Co-morbid conditions reported by IBS patients include fibromyalgia, migraine headache, joint hypermobility syndrome, temporomandibular joint disorder, bladder pain syndrome/interstitial cystitis, anxiety and depression.[81-83] All of these conditions have a female predominance in the general population and many have a pain component.

Among women with FGIDs a number of female specific conditions are more common when compared to non-FGID groups. These include dysmenorrhea, endometriosis, adenomyosis, leiomyomas, pelvic floor myalgia, vulvodynia, chronic cyclic pelvic pain, dyspareunia, dysmenorrhea, and polycystic ovary syndrome. Dyspareunia and sexual functioning in women with IBS remain understudied problems. Hysterectomy is 3-fold higher in women with IBS[84] suggesting that the overlap with gynecological conditions may contribute to greater health care seeking and subsequent surgical intervention.

Several mechanisms may account for the comorbidity in women with FGIDs, particularly IBS. These include brain activation patterns, dysregulation of the hypothalamic-pituitary-adrenal axis, immune dysfunction, visceral and somatic pain sensitivity alterations, autonomic nervous system dysregulation, and genetic susceptibility. Because the etiology and pathophysiology of each of these conditions are likely complex and multifactorial a single common pathogenesis has remained elusive. Other factors, including access to health care and health care seeking behavior, may also contribute to gender differences in diagnosis of comorbid conditions. The type, number, and duration of comorbid conditions may contribute to the toll of interpersonal stress.

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GENDER AND PATHOPHYSIOLOGY

PRE-CLINICAL

Visceral Pain Perception

Under basal conditions, most studies have found that normal cycling females have a greater response than males to visceral pain stimuli.[85, 86] Genetic background clearly has a role since the strain of rodent determines which sex is more sensitive to noxious visceral stimuli.[87] Visceral pain can be enhanced by chemical irritation, inflammation, and stress. Generally all of these insults either show no sex difference or greater pain responses in female animals than males.[85] Stress, particularly repeated stress and early life stress, also produces visceral hyperalgesia days or even months after the stress period, with female rodents being significantly more susceptible.[88, 89]

The role of sex hormones in visceral pain has received considerable attention and produced much controversy. Studying natural variations in sex hormones in female rodents is complicated by a much shorter (4-6 days) estrus cycle with smaller changes in the plasma estrogen and progesterone levels than in women.[90] Since studies evaluating the effect of the estrus cycle in rodents have produced conflicting results,[85, 91, 92] many investigators have resorted to ovariectomizing female rodents and comparing the effect of estrogen and progesterone replacement. This strategy too has resulted in conflicting observations that are probably due to the time between ovariectomy and pain testing, the dose of estrogen/progesterone and whether it's administered abruptly with a single dose or at a slow constant rate.[85, 93] The fact that estrogens can act rapidly by binding to estrogen receptors located in the plasma membrane, in addition to their slow effects mediated by gene expression[94] may explain some of these differences.

Somatic pain perception

A great deal more preclinical work has been done on sex differences in somatic pain in animals with more equivocal results than visceral pain. Sex differences, if found at all, depend on the specific modality being tested (thermal, mechanical, chemical, electrical), the location or dermatome involved, and the experimental model (acute, neuropathic, ischemic, inflammatory pain).[95] Again genetic background

seems to play an important role in determining which sex is more sensitive since different strains of mice and rats can produce opposite effects using the same pain test.[95] The role of specific receptors and gene polymorphisms in sex-specific visceral and somatic pain responses is accumulating.[86, 92]

Motility and Permeability

Both estrogen and to a lesser extent progesterone affect GI motility and colonic permeability.[92] Treatment of ovariectomized rats with the combination of estrogen and progesterone results in slower colonic transit,[96] possibly mediated by effects on nitric oxide-containing neurons in the myenteric plexus[97] and the number and function of mast cells in GI mucosa.[98] In addition, stress has a greater effect on decreasing upper GI motility and increasing lower GI motility in female compared to male animals.[99, 100] This effect is likely mediated by corticotropin-releasing factor receptor-1 which are potentiated by estrogen and expressed by colonic myenteric neurons.[101] Estrogen also contributes to the maintenance of the intestinal barrier that serves an important role in the body's defense against pathogens. The positive role of estrogen in maintaining intestinal barrier function may be through maintenance of tight junctions and/or influence on inflammatory response.[102]

CLINICAL

Abdominal Symptoms

In the general population, women are more likely to report abdominal pain and pain-related IBS diagnostic symptoms (e.g. pain relieved by defecation),, while in the IBS population, the prevalence of pain-related symptoms does not vary by gender. In addition, IBS women report more constipation, straining, bloating, and abdominal distention, and men reporting more diarrhea-related symptoms, including increased stool frequency.[103]

Visceral pain perception

There is no conclusive data to suggest gender influences visceral pain perception or the referral of pain to GI stimulation in healthy and FGID subjects.[104-108] Women, however, are more likely to exhibit increased sensitivity following repetitive sigmoid distention than men with IBS.[107, 109] Reasons for inconsistencies across studies may include study design, small subject numbers and techniques, ovarian hormone and receptor levels, and/or stress levels, mood, vigilance, and early-life and social factors.

Somatic pain perception

Studies suggest that healthy women tend to exhibit greater somatic pain sensitivity than men.[86] In FGIDs, studies are scarce with only one study in IBS suggesting that thermal sensitivity does not differ between sexes.[110] Variability between studies is probably for similar reasons discussed for visceral pain perception.

Motility

Esophageal anatomy and innervation do not appear to differ significantly by gender, and only minor gender-specific differences have been reported in esophageal motor function.[111] Slower gastric emptying rates of both solids and liquids have been shown in females compared to males.[112-116] Postprandial proximal gastric relaxation was prolonged and perception scores increased in women compared with men.[117] Studies have found colon transit times to be shorter in men than women, particularly in the right colon.[118-120] Rao et al, using ambulatory 24-hour colonic manometry, found pressure activity in the colon of healthy women to be reduced compared with age-matched men.[121] Phase of menstrual cycle was not controlled in these studies. There are no published non-drug studies comparing colonic motility in women and men with IBS. Anal sphincter pressures, anal pressures during maximum sphincter contraction, and volumes required to induce a desire to defecate have been reported to be lower in women.[122, 123]

Cardioautonomic Tone

Autonomic nervous system (ANS) dysfunction has been reported in patients with IBS.[124] However, few studies have evaluated gender differences in measures of autonomic function other than GI motility in persons withIBS. Cheng and coworkers reported significant blunting of the ANS response to flexible sigmoidoscopy (a visceral stressor) in IBS compared with controls, and that overall women had higher cardiovagal tone and lower cardiosympathetic balance compared to men.[125]

Central Processing of Visceral Stimuli

Healthy subjects: Using functional magnetic resonance imaging (fMRI), Kern et al[126] demonstated greater response to rectal distension in sensory and affective regions (dorsal anterior cingulate cortex, prefrontal cortex and insula cortex) in females compared with males. In contrast, Berman et al[127] found a trend for greater activation of the insula, and anterior and midcingulate cortex to rectal distension in men compared with women. A more recent fMRI study reported greater activity in the dorsolateral prefrontal cortex and middle temporal gyrus during anticipation of rectal pain, and in the cerebellum and medial frontal gyrus during painful rectal stimulation in women compared with men.[128] Although a study using magnetoencephalography while recording cortical evoked potential to painful esophageal stimulation reported no sex difference,[129] sex differences in brain response to esophageal pain have been observed.[130] Despite no significant differences in psychophysiological factors known to influence brain processing, such as anxiety, personality type, autonomic response to pain, and pain perception levels and thresholds, women compared to men exhibited a greater decrease in amygdala activity during anticipation of esophageal pain and a greater increase in midcingulate cortex and anterior insula activity during esophageal pain.[130] These observations were interpreted as women having greater engagement of cognitive coping strategies to the anticipation of visceral pain, and greater emotional response during actual esophageal pain.[129]

FGID subjects: Initial brain imaging studies using rectal balloon distension in IBS patients found that male patients exhibited greater activation compared to female patients of the insula,[131, 132] as well as dorsolateral prefrontal cortex and dorsal pons/periaqueductal gray.[132] In contrast, female IBS patients

demonstrated greater activation of the ventromedial prefrontal cortex, right anterior cingulate cortex, and left amygdala compared with male patients.[132] These data suggest female patients have greater activation of affective and autonomic regions, while males show a greater activation of regions in corticolimbic pain inhibition system. A follow-up study using connectivity modeling of the same data suggested that the differences between men and women are mainly due to differences in the effective connectivity of emotional arousal circuitry rather than visceral afferent processing circuitry (Figure 2).[133]

More recent neuroimaging studies have demonstrated brain activity/connectivity differences between men and women, even in the absence of a noxious stimulus (eg, rectal distension). Female IBS patients have shown higher frequency power of the insula compared with male patients.[134] Although sex differences were seen in healthy controls in the resting state, oscillatory dynamics of emotional arousal regions (amygdala and hippocampus) were exaggerated in IBS patients, mainly due to an increased high frequency power in female patients.[134] Furthermore, sex differences in the resting state oscillatory dynamics of sensorimotor regions seen in healthy subjects (greater low frequency power in men) were reversed in IBS patients with greater low frequency power in women.[134] A second resting state study demonstrated sex differences in the functional connectivity between the dorsal anterior insula (INS) and medial pre-frontal cortex (PFC) and precuneus in IBS are similar to healthy subjects, but more enhanced.[135] These findings may relate to females dedicating more resource allocation to interoceptive awareness, while males rely more on cognitive processes with IBS placing further stress on this bias. Finally, sex difference in the impact of early adverse life events (EALs) on resting state brain connectivity has been demonstrated in IBS patients.[136] EAL scores were associated with greater connectivity of thalamus, insula, anterior cingulate cortex, and middle temoral gyrus with the cerebellar network in men only. The cerebellar network is involved in fear perception, motor function, and visual-motor learning, as well as physical and psychological pain. The functional consequences of these sex-specific alterations in cerebellar network alterations remain unknown.

Sex differences in structural changes of the brain in IBS have also been demonstrated. Female patients have demonstrated significantly less cortical thickness in the right subgenual anterior cingulated

cortex than male patients.[137] Moreover, using diffusion tensor imaging, reduced integrity of sensorimotor and descending pain modulation pathways has been demonstrated in female compared with male IBS patients. Such differences were not seen in healthy subjects.[138]

Genetics and Immunologic/Microbiome

Multiple factors including genetics, the environment, sex hormones and the gut microbiota may modulate the immunologic response to inflammation and infection.[88] Our understanding of the role of inflammatory factors in FGIDs and genetics especially IBS is rapidly increasing. The use of new 'omics' approaches will need to consider sex as a potential factor in terms of understanding new metabolomics and transcrioptomics findings. Further research is needed to clarify the potential relevance of these factors in immune system dysregulation and FGIDs.

Emerging evidence suggests that interactions between gut microbiota and altered immune function may play a role in the pathogenesis of IBS , and several studies support the importance for immune activation in the pathophysiology of post-infectious IBS.[139] Female gender in both adults and children has been reported as a risk factor for developing IBS symptoms following infectious gastroenteritis.[140, 141] The gut bacteria are modulated by sex steroid hormones, in particular estrogen. In addition, gut bacteria can influence the metabolism of estrogen (Figure 3).[142] Flack and colleagues first proposed the concept of 'microgenderome', the bidirectional interaction between sex hormones and the microbiota.[143]

GENDER AND TREATMENT RESPONSE

Clinical Assessment

The clinical implications of gender are relevant in both the diagnosis and clinical management of FGIDs. Beginning with the history, IBS-like symptoms are often present in gynecological conditions, the most serious of which are ovarian and endometrial cancer and should be included in the initial differential diagnosis. Asking the patient when symptoms started may provide important information about etiology

and subsequent approaches to management. There are history and examination features unique to women: menstrual history, gynecological surgery, bimanual pelvic examination. The comorbidity of IBS with gynecological pain conditions and pelvic floor dysfunction warrants careful examination. In the differential diagnosis, clinicians should avoid mistakenly employing the gender-prevalence to influence a premature diagnosis of a FGID.

Psychological Treatment

Whether gender makes a difference to outcomes with psychological therapy is unclear since women outnumber men in most FGID treatment trials.[144] These trials have not been sufficiently powered or included sub-analyses to determine whether or not there is a differential response to treatment between genders.[145, 146]

There is no gender bias in outcomes with cognitive behavioral therapy, psychological therapy or emotional awareness training for IBS,[147] and gender was not selected into a predictive model of treatment response. By contrast, Guthrie and colleagues[148] reported minor advantages for women in response to therapy compared to men, but gender was not selected into their final analysis model. For individual psychotherapy in patients with functional dyspepsia and severe IBS,[149] efficacy is similar to selective serotonin reuptake inhibitor therapy with no gender difference in outcome with either treatment.

Two evaluations of hypnotherapy[150, 151] gave contrasting results with respect to gender. An audit of 1,000 IBS patients who met Rome II criteria (80% female) for IBS and underwent hypnotherapy for 3 months found that 80% of women improved compared to 62% of men.[151] A study of 250 participants noted a poor response in men with IBS with diarrhea.[150] By contrast, a randomized controlled trial,[151] albeit in a smaller population, demonstrated that gender, age, disease duration, and IBS type had no influence on the long-term success of hypnotherapy.

Pharmacologic Treatment

Psychotropic Agents. A recent systematic review of antidepressant therapy identified that most studies did not conduct separate analyses by gender.[146]

Gut-Directed Agents. A number of small, variable quality studies have been subject to meta-analysis[152] and shown modest benefits over placebo for fiber, anticholinergics, and peppermint oil, but no separate analysis of gender difference was undertaken.

Therapies targeted at serotonin (5-HT) receptors in the gut seem to have a differential effect in men and women. Alosetron, a 5-HT_3 antagonist, providing 26-40% adequate relief of pain response rate in women, gives 33% pain decrease in men at the same dose.[153] The basis for this gender difference is not clearly established. Alosetron is more effective in slowing colonic transit,[154] attenuating the gastro-colonic response, and increasing rectal compliance[155] in women than men.

Three large series[156] of prucalopride, a highly selective $5HT_4$-agonist, recruited 85% female patients and demonstrated equal efficacy in both sexes. For other drugs commonly used to treat motility disturbance (domperidone, opioid-based constipating agents, laxatives, probiotics), there is no evidence of a gender-related difference in efficacy.[157]

Most medications for FGIDs are cleared through the cytochrome P450 pathway that can be affected by female sex hormones. While women clear drugs more quickly than men through this pathway, this is balanced by the difference in body size and adiposity of women. There have been no clinically significant differences in the pharmacokinetics of FGID drugs, and hence, dosages need not be adapted by gender.

LIFE STAGES AND AGING

The FGIDs affect people across the spectrum of age. Some FGIDs increase with age while others decrease. Some begin in childhood while others start after developmental stages including puberty and

menopause. The trajectory of many FGIDs are unknown due to lack of long term follow up. Cohort studies with pre-identified clinical and biological markers may yield important information about the normal GI tract aging in concert with the evolution and progression of FGIDs.

Extensive epidemiological data exist for IBS, dyspepsia, heartburn, constipation, and fecal incontinence, but less is known about the other FGIDs. The presence of FGIDs in children is well recognized. The exact age of onset of FGIDs remains to be determined. A link between childhood IBS and adult IBS remains to be established.

Both laboratory animal and human data indicate that EALs may contribute to either increased visceral sensitivity later in life and/or potentially visceral and somatic conditions.[24] While EALs results in higher rates of IBS in both genders, women appear to be more susceptible to the development of pathologies following exposure to EALs.[89]

Approximately 70-95% of women report heartburn, nausea or vomiting during their pregnancies. Most episodes of heartburn occur during the first and second trimester.

The perimenopause is defined as the period of transition to menopause. In a cross-sectional study of premenopausal and postmenopausal women with IBS, there were more GI symptoms in early post-menopausal women compared to premenopausal women.[158] Menopause is the cessation of a woman's reproductive ability. Understanding the effects of menopause on FGIDs is confounded by the effects of aging, the presence of co-morbid conditions, and medication use (ie, hormone replacement use (HRT)). In one study using the General Practice Research Database in the UK, investigators found that current and past users of HRT had an increased risk (incidence 1.7 in non-users and 3.8 among users) of IBS compared to non-users.[159]

Overall the prevalence of IBS decreases with age in both men and women.[160] The existing literature is discordant with regard to the changes in the estimates of bloating by age.[32] Most studies find that the prevalence of constipation increases with advancing age,[63, 64, 161] Less is known regarding functional diarrhea, although one study identified decreasing rates of diarrhea with age.[46]

There is some evidence to suggest that with aging there is reduced biodiversity. However, it is difficult to separate out changes that are related to aging, per se, or lifestyle, history of antibiotic treatment, hospitalization, and frailty. Reductions in fiber intake due to poor dentition, decreased saliva production, reduced economical resources may also contribute to age-related changes in microbiota composition.

Fecal incontinence has been extensively studied and increases with age. Data from the Nurse's Health Study show that 4% of women age 62 to 87 have fecal incontinence and 7% have both urinary and bowel incontinence.[162]

METHODOLOGICAL ISSUES IN FGIDS

As a result of methodological issues limiting interpretation of studies, there remain many unanswered questions concerning gender, age, and patient's perspective in FGIDs. Due to the female predominance and greater likelihood of women to participate in research studies, there are insufficient numbers of male participants to make meaningful interpretations and adequately assess gender and sex differences in psychological, physiological, and treatment studies. Given the intersection of gender and socioeconomic factors in women's health the environment, relationships, and resources (eg, socioeconomic status) need to be considered when assessing gender differences. Another major methodological concern is that most studies use a cross-sectional design which limits the more comprehensive understanding of the pathogenesis, development, course and impact of these disorders in men and women.

Many physiologic studies utilize relatively small sample sizes and do not account for psychosocial variables, overlapping FGID or co-morbidities, abuse history or EALs, and therefore, may not apply to the general patient population. These studies may be influenced by the selection bias of participants who are willing to undergo invasive research protocols.

Translating the various mechanisms of pain and GI function from animal studies to humans is challenging. Differences in the type and strain of the animal model and type of stressor, if used, need to be taken in account when interpreting these studies.

Similarly for women, the menstrual cycle needs to be considered in studies. In most studies, menstrual phase is frequently not determined, or is assessed by the count forward/backward method and not by measuring the luteinizing hormone surge or ovarian hormone levels to more accurately assess the follicular and luteal phases. Other confounding methodological issues include the use of oral contraceptive agents, HRT and pre vs. postmenopausal status in women. The impact of the transition from a premenopausal to perimenopausal state to menopause remains unknown.

Most studies examining psychological factors have focused on anxiety and depression and, to a lesser extent, personality traits. Other aspects of psychological functioning such as quality of relationships, social support, health perceptions, traumatic and stressful events, and effects of childhood experience other than abuse have been largely ignored in studies comparing men and women.

Adequate sample sizes of each gender, particularly men, and comparable treatment doses must be obtained to determine if men and women respond similarly to treatment. There may be gender bias in the placebo response. Patients for clinical trials are generally recruited from specialty practices where women are more likely to be referred than men, thus compounding problems of selection bias.

Future studies will need to have adequate numbers of men with gender-related variables such as history of EALs, abuse, anxiety, or depression.[19] At the same time, greater attention needs to be given to transgender men and women.

In summary, this review emphasizes: (1) the importance of the patient's experience and perspective, (2) the influence of society, culture, gender, and age on all aspect of the individual's experience, (3) the influential role of an individual's sex on the biologic and physiologic processes of brain-gut interactions, and (4) the potential of the health care provider in influencing patient outcomes.

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FIGURE LEGEND

Figure 1. **Odds ratio for irritable bowel syndrome (IBS) in women vs. men according to geographical location**. Data are grouped according to the geographic region. Numerically higher ratios are reported from the Western world.[48]

Figure 2. Estimated effective conductivity differnces between men and women in proposed network comprising the "homeostatic-afferent", "emotional-arousal", and "cortical-modulatory circuits". The operation of the proposed network (as estimated by the completely unconstrained model) during Baseline, Inflation, and Expectation (columns) is presented for females (top rows) and males (bottom rows). The beta coefficients (effective connectivity) are depicted by the thickness and color of the arrows. Solid arrows represent a parameter estimate that was considered significantly different from zero whereas dashed lines represent nonsignificant coefficients. Panel A depicts positive coupling whereas Panel B represents negative coupling. Amyg: Amygdala; iACC: infragenual cingulate cortex; INS: insula; LCC: locus coeruleus complex; mOFC: medial orbital frontal cortex; sACC: supragenual anterior cingulate cortex.

Figure 3. Sex hormones in the mutual brain-gut-microbiota interactions. Sex hormones influence peripheral and central regulatory mechanisms involved in the pathophysiology of IBS 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.

TABLES

Table 1. Gender Differences of History of Sexual, Physical and Emotional Abuse in Persons with and without IBS

Author (Year)	Early life events	Findings	Gender differences within group comparisons
[25]	Childhood abuse, Sexual abuse	A history of sexual abuse was more common in women than in men but the authors did not differentiate between patients with or without IBS.	Not addressed
[26]	Severe lifetime sexual trauma, severe childhood sexual abuse, lifetime sexual victimization	All of the IBS patients studied that reported a history of sexual abuse were female.	Women > men
[24]	General trauma, physical punishment, emotional abuse, and sexual events	Significant differences were observed mainly in women with IBS. Various types of early adverse life events are associated with the development of IBS-particularly among women.	Women > men
[27]	Childhood abuse	No significant association of childhood adversity with the likelihood of developing IBS in either men or women.	No differences
[28]	Childhood abuse	A history of child abuse was similar in case and control group. But the authors did not differentiate between patients with or without IBS.	Not addressed

IBS: irritable bowel syndrome

Table 2. The Effect of Sex and Age on the Prevalence of FGID

FGID	Effect of sex	References for sex	Change with age	References for age
Esophageal				
Globus	F>M	[32] [49]	↓	[32] [49]
Rumination	F=M	[32]	↓	[32]
	F>M	[34] [35]		
Functional chest pain	F=M	[49] [36] [50]	↓	[32] [49]
	F>M(at tertiary care)	[37]		
Functional heartburn	F=M	[49] [51]	=	[32]
Dysphagia	F>M	[32] [49]	↑	[32]
Gastroduodenal				
Dyspepsia	F=M	[32] [39] [40]	↓	[52] [46] [53]
Aerophagia	M>F	[32]	↓	[32]
	F > M	[54] [45]		

Functional vomiting	F=M	[46]	↓	[46]
Biliary tract	F > M	[32] [55]	↑	[32]
Lower GI tract				
IBS	F > M	[56] [32] [25] [47] [29] [57]	↓	[32] [58] [59]
Functional constipation	F>M	[56] [32] [46] [60] [30] [61] [62]	↑	[63] [64]
Functional diarrhea	M>F	[32] [46] [60] [30] [48] [65]	↓	[46]
Functional bloating	Discordant	[32]	Discordant	[32]

	F>M	66 67 48		
FAPS	F>M	32 68	↓	32
Fecal incontinence	F>M(at home)	69	↑	
	M>F (nursing homes)	71		70 64
Functional anorectal pain	F>M	32	↓	32
Outlet delay	F > M	72 73 74 75	=	72

FAPS: functional abdominal pain syndrome; FGID: functional gastrointestinal disorders; GI: gastrointestinal; IBS: irritable bowel syndrome.