Ther Adv Gastroenterol
2020, Vol. 13: 1–11
DOI: 10.1177/1756284820915043

Sex-based differences in inflammatory bowel diseases: a review

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***Abstract*:** Sex-based differences in inflammatory bowel disease (IBD) pathogenesis, disease course, and response to therapy have been increasingly recognized, however, not fully understood. Experimental and translational models have been leveraged to investigate hypothesized mechanisms for these observed differences, including the potential modifying role of sex hormones and sex-dependent (epi)genetic and gut microbiome changes. The primary objective of this review is to comprehensively describe sex-based differences in IBD including epidemiology, pathogenesis, phenotypic differences, therapeutic response, and outcomes.

Keywords: Crohn's disease, gender, natural history, ulcerative colitis

Received: 29 November 2019; revised manuscript accepted: 3 March 2020.

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Introduction

The inflammatory bowel diseases (IBDs), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic and oftentimes progressive inflammatory diseases of the bowel.[1,2] The clinical course of IBD is unpredictable, but generally includes periods of remission interspersed with periods of acute or subacute exacerbations, so-called 'flares,' the triggers for which are multiple. Extraintestinal symptoms might accompany the gastrointestinal (GI) symptoms, or present seemingly independent of luminal symptoms. Although it is well established that IBD pathogenesis represents the complex interplay of genetic susceptibility and dysregulated innate and adaptive immune systems in the face of environmental triggers, and likely gut dysbiosis, the 'unpredictable' nature of IBD reflects our still incomplete understanding of the interaction of these elements, and possibly others yet to be defined.[1,2]

Sex-based differences in IBD pathogenesis, disease course, and even response to therapy have been increasingly recognized. Our ability to leverage experimental and translational models to define and test hypothesized mechanisms for these observed differences has already extended our understanding of possible mechanisms underlying observed differences, including the potential modifying role of sex hormones and sex-dependent (epi)genetic and gut microbiome changes. That other immune-mediated diseases, such as rheumatoid arthritis, scleroderma, and systemic lupus erythematosus,[3–6] similarly have sex-based differences in incidence, as well as natural and therapeutic disease course provides additional support that observed sex-based differences have a biological basis. That said, sex-based differences that are nonbiological, including differential access to care and differential early-life exposures and throughout-life exposures, must also be considered and might be particularly relevant in IBD. Further complicating our understanding of observed sex-based differences in IBD is the striking geographic differences, specifically between Asian–Pacific and Western countries.[7,8]

Better understanding the epidemiology of sex-based differences in IBD, including disease presentation and response to therapy, as well as defining the underlying biological and nonbiological mechanisms, has far-reaching clinical, scientific, economic, and societal implications. Herein, our primary objective is to comprehensively review sex-based differences in IBD, including epidemiology, pathogenesis, phenotypic differences, therapeutic response, and outcomes.

Wherever relevant, we also summarize complementary experimental data and data from other immune-mediated diseases where sex-based differences are similarly recognized.

Search strategy

To identify relevant literature, we searched PubMed for the following key terms, including "inflammatory bowel disease," "Crohn* disease," "ulcerative colitis," "sex, "gender," "phenotype," "surgery," "efficacy" along with different drug types such as antitumor necrosis factor drugs (anti-TNFs), antibiotics, thiopurines, and 5-aminosalicylates (date of search 21 October 2019). The search yielded 793 studies, which were screened based on title and abstract and, if deemed relevant, the full text was reviewed. We additionally searched the cited references of all included studies to identify any additional relevant articles.

Sex-based differences in IBD epidemiology

IBD incidence

Two recent pooled cohort analyses demonstrated sex-based differences in age of IBD onset in Western and Asian–Pacific countries.[7,8] Based on population-level data from 16 Western countries, females have a lower risk of CD compared with males until puberty, at which point there is a reversal, with females having a higher risk.[7] Generally speaking, males and females demonstrated similar incidence of UC before age 45; however, above age 45 years, males demonstrated higher risk of incident UC than females. Using a similar analytic approach for population-based data from 12 Asian–Pacific countries, the authors[8] demonstrated a male predominance in CD risk, with males having a higher risk of incident CD starting in adolescence and persisting until age 50 years. In addition, in contrast with Western populations, there was a male predominance of UC from adolescence until age 65 years, after which UC incidence rates were similar between males and females.

IBD type and phenotype

CD manifests in a variety of phenotypes, from mild ileitis to stricturing disease to perianal fistulizing disease, in any portion of the gastrointestinal tract. UC, on the other hand, has less phenotypic variability, and, by definition, only involves the colon. While not fully understood, phenotype is relevant for gauging natural disease course and prognosis and, relatedly, is critical for guiding therapeutic decision making.[9] One observational cohort of 541 patients with CD found that, compared with males, females experienced earlier disease onset and more frequent extraintestinal manifestations (EIMs), particularly arthritis, *erythema nodosum* (EN) and ocular manifestations.[10] The need for surgery was high in this cohort, irrespective of sex, and with no apparent differential risk in males *versus* females; however, the time between surgery and disease recurrence was significantly shorter in females *versus* males (4.8 *versus* 6.5 years, $p = 0.04$). Of note, this study was conducted before the era of biologic therapies and might be one explanation for the high surgical rates reported.

A more recent prospective study combined together two Dutch multicenter observational cohorts and analyzed differences between patients with CD or UC according to sex.[11] Early-onset CD occurred more frequently in males. Again, EIMs, including arthritis, skin, and ocular manifestations, arthropathy, and osteopenia occurred more frequently in females. Males had ileal disease and required ileocolic resection more frequently. One US-based cohort study demonstrated that female sex was a risk factor for nonfistulizing perianal CD (i.e. skin tags, anal strictures, anal fissures, and deep anal-canal ulcers).[12]

Collectively, these studies suggest that pediatric CD might be more common in males, but there is a shift to female predominance, at least in Western countries, around puberty, and this might plausibly relate to sex-hormone-dependent mechanisms. Data are mixed, and overall, limited, with respect to sex-based differences in phenotypic manifestations of CD and UC.

Sex-based differences in IBD pathogenesis

The etiopathology of observed sex-based differences in IBD is multifactorial and complex, implicating sex-based differences in both environment and genetics, as well as their interaction. As noted above, a complicating factor is sex-based nonbiological differences in exposures, including early-in-life exposures. Several genetic susceptibility loci for both CD and UC have been identified on the X chromosome.[13–15] In particular, haplotypes

of Toll-like receptor 8 have been identified; these are also associated with other autoimmune diseases with female predominance.[13,14] Several studies have demonstrated that the R30Q DLG5 variant is associated with a reduced risk of CD among females but not males.[16–18] Regarding UC risk, a variant of the interleukin 23 (IL-23) receptor is associated with a reduced risk of UC in females but not in males,[19] while a variant of the IL-10 receptor is associated with increased UC risk in females but not males.[20] Moreover, sex hormones, particularly estrogens, and the fluctuation with age and critical phases such as puberty and menopause, might induce epigenetic changes that contribute to the differential pathogenesis and epidemiology of IBD.[7,8,21,22] That sex-based differences in familial risk of IBD are also observed further implicates genetics.

A recent retrospective study compared two cohorts of patients with either familial or sporadic IBD and demonstrated a female predominance among familial IBD cases (61% *versus* 54%, $p=0.011$).[23] The proportion of mother-to-child CD 'transmission' was greater than father-to-child CD 'transmission' (55% *versus* 32%, $p=0.018$). Furthermore, among the children of parents with IBD, female-to-female transmission was greater than female-to-male (36 *versus* 18, $p=0.02$). These findings suggest that female sex-specific epigenetic factors, including imprinting, are contributory.

Estrogens play a multifactorial role in inflammation and autoimmune diseases.[24] Experimental data implicate estrogens in gastrointestinal physiology, probably *via* estrogen receptor (ER) beta.[25–28] In rat models, ERbeta signaling alters colonic epithelial permeability, and reduced ERbeta messenger ribonucleic acid (mRNA) expression is associated with active colitis.[29] However, ERbeta expression was associated with a decreased risk of dextran sulfate sodium (DSS)-induced colitis only in female, but not male, mice.[30] Recent human data also implicate ERbeta expression in the clinical presentation of IBD, with one study demonstrating that patients with active IBD had lower ERbeta receptor expression compared with both healthy controls and those whose IBD is in remission; this study did not evaluate differences based on age or sex, however.[31] ERbeta expression might also be associated with therapeutic response to antitumor necrosis factor (anti-TNF) therapy,[31] and thus might be relevant when considering sex-based differences in therapeutic responses.

Dendritic cells, which are important for establishing host tolerance to foreign antigens and T-regulatory-cell development, might also be relevant. Dendritic cells have increasingly been investigated for their role in IBD pathogenesis, specifically CD, as these cells are decreased in mouse models of Crohn's ileitis (SAMP1/YitFc mice).[32] Goodman and colleagues[33] demonstrated that female SAMP1/YitFc had less T-regulatory cells in the gut lymphoid tissue compared with their male counterparts. Interestingly, the authors[33] also demonstrated that female SAMP1/YitFc mice did not experience the same magnitude of protective effect with exogenous estrogen administration as males.

Sex-based differences in the gut microbiome have been implicated in a variety of other diseases, and now more recently IBD. Indeed, this hypothesis is well-grounded, given the microbiota's critical role in IBD pathogenesis related to immune regulation, and dysregulation.[34] Experimental data in mouse models of IBD and other immune-mediated diseases demonstrate sex-based differences in gut microbiome composition, including marked differences after gonadectomy and hormone replacement therapy.[35–37] Although autoimmune diseases in general occur more commonly in female patients, germ-free mouse models of type 1 diabetes show a reduced predilection for development of the disease in females *versus* males.[38] The microbiota in these mice differed by sex, and this was reversed by male castration.[38] Colonization with some microbes over-represented in male mice (e.g. *Enterobacteriaceae* and segmented filamentous bacteria) was associated with a reduced risk of type 1 diabetes, suggesting that hormones and microbe expansion may result in a positive feedback mechanism that contributes, at least in part, to sex-based differences in autoimmune- and immune-mediated diseases. Interestingly, when microbiota from adult male, nonobese diabetic mice were transferred to immature female, nonobese diabetic mice, there were higher levels of circulating testosterone and lower levels of inflammatory markers, with demonstrated reduced risk of type 1 diabetes among females.

Innate hormone fluctuations are also relevant in IBD pathogenesis and clinical course.[39] A

case-control study from the Nurses' Health Study cohort found that lower prediagnosis endogenous levels of testosterone were associated with increased risk of CD but not UC.[40] Additional evidence for exogenous sex hormones comes from several studies demonstrating increased risk of IBD with oral contraceptive pill (OCP) use and hormone replacement therapy.[41–44] A meta-analysis of 14 studies published in 2008 demonstrated that OCP use was associated with 51% higher odds of CD [odds ratio (OR) 1.51, 95% confidence interval (CI) 1.17–1.96] and 53% higher odds of UC (95% CI: 1.21–1.94).[45] These estimates were attenuated after controlling for smoking status, with an OR of 1.46 (95% CI 1.26–1.70) for CD and OR 1.28 (95% CI 1.06–1.54) for UC. An updated meta-analysis published in 2017 demonstrated slightly lower increased risk, although the exposure to OCPs remained significant (OR for IBD overall 1.32, 95% CI 1.17–1.49).[46]

Environmental exposures

The risk of IBD associated with environmental exposures also varies according to sex, although data are somewhat heterogeneous. Environmental exposures in general are difficult to study, since many factors must be considered, including timing of exposure, duration, and dose of exposure. For example, tobacco use has been associated with increased endogenous levels of sex hormones in both pre- and postmenopausal women.[47,48] There are also gender disparities in tobacco use worldwide, but these rates vary by country.[49,50] These differences might contribute to sex-based differences in IBD epidemiology as well as observed regional differences. Unfortunately, the majority of studies control for sex and do not provide sex-stratified risk of IBD associated with environmental exposures, particularly early-in-life exposures (e.g. antibiotic exposure, breastfeeding), but this will be critical in future investigations for expanding our understanding of sex-based differences in IBD.

In addition to innate and environmental exposures, there are also disparities in access and utilization of healthcare by sex that must be considered.

Sex-based differences in IBD clinical presentation

IBD flares

Hormone fluctuations are also associated with flares or changes in disease activity, albeit with some mixed data that likely reflect study design and study population differences. Rolston and colleagues[51] recently reported findings from a large survey of female patients who were asked about their symptoms around menses and pregnancy. Based on the survey results, over half of women with IBD have worsening symptoms around their menses. Women with UC, compared with CD, more often experienced worsening symptoms during pregnancy ($p = 0.02$).[51] A separate, small retrospective cohort analysis demonstrated that hormone replacement therapy among postmenopausal women was associated with reduced frequency of flares, although there were no differences in disease activity among pre- *versus* postmenopausal women.[52] These findings are in contrast to a larger, multicenter retrospective study of both men and women with IBD that demonstrated a twofold increased risk of IBD flare associated with hormone therapy following a diagnosis of prostate or breast cancer.[53] Unfortunately, the risk was not reported separately among men *versus* women. The data regarding the role of male sex hormones in IBD pathogenesis and disease course are sparse and warrant investigation.

EIMs

As noted above, there are observed sex-based differences in EIM epidemiology and, presumably, pathogenesis. Primary sclerosing cholangitis (PSC) is a poor prognostic comorbid condition of the biliary tree most commonly associated with UC. Literature consistently supports a male predominance for PSC, including a recent, large, international retrospective cohort study of patients with PSC, 65.5% of whom were male; unfortunately, the underlying etiology for this predilection remains elusive.[54–56]

EN and *pyoderma gangrenosum* (PG) are two classic skin conditions associated with IBD, with EN occurring in 3% (UC) to 6% (CD), and PG in 2% of IBD patients.[57] Female sex is independently associated with these two conditions.[58] Relatedly, postoperative peristomal PG occurs with higher frequency among females *versus* males.[59]

Inflammatory arthritis is another IBD-associated EIM.[60] The pathogenesis is not fully understood but might be related to the microbiome of both the gut and skin. Based on a nationwide Danish registry case-control study of patients with IBD (cases) and matched controls, there was an

increased risk of concomitant inflammatory arthritis in all patients with IBD, which was more pronounced among females.[61] Additional relevant findings from this study were that patients with either CD or UC had an increased likelihood of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. When stratified by sex, the odds of rheumatoid arthritis remained significant for females with CD and UC, but not for males (OR for CD 2.3, 95% CI 1.7–3.0; OR for UC 1.7, 95% CI 1.4–2.1). The odds of psoriatic arthritis remained significant for females with UC only, but not for males (OR 2.0, 95% CI 1.3–2.8).

Sex-based differences in IBD-related clinical outcomes

Therapeutic response

Over the past 2 decades there has been an exciting increase in the number of new medical therapies for IBD; several with different mechanisms of action and therapeutic targets that are being rigorously tested in clinical trials and approved for clinical use. Current therapeutic classes include biologics, small-molecule inhibitors, immunomodulators, steroids, and 5-aminosalicylic acid (5-ASA) formulations. Selection of therapy depends on disease phenotype, course, disease severity, disease complications, and patient-specific factors, including preference. Unfortunately, despite mounting evidence that sex hormones impact the natural course of IBD, very few studies have investigated how sex modulates therapeutic response and, generally speaking, data are extremely limited on therapeutic response of IBD to medications, stratified by sex.

Some studies have evaluated patient response to biologics by sex using heterogeneous study designs, and the results are mixed. A systematic review of 39 studies evaluating loss of response to adalimumab found that male sex was associated with higher likelihood of loss of response and need for dose escalation.[62] By comparison, one single-center retrospective cohort analysis of 210 patients with CD treated with infliximab found that male sex was associated with 66% reduced risk [hazard ratio (HR) 0.34, 95% CI 0.15–9.74] of failure of clinical response.[63] A smaller retrospective cohort study of 47 patients with UC treated with infliximab reported no sex-based differences in response to infliximab, although inadequate power must be considered due to sample size.[64] This is in contrast to a study of 125 patients with steroid-refractory UC demonstrating that, compared with males, females experienced a 3.5-fold higher likelihood of long-term remission when treated with infliximab (OR 3.46, 95% CI 1.41–8.46).[65] Among 265 Swedish patients with either UC or CD, treated with vedolizumab, female *versus* male sex was associated with a higher rate of drug termination due to 'intolerance' (HR 2.86, 95% CI 1.17–6.99); however, because this study was based on data from a nationwide registry, no individual-level details were available, so the reasons for intolerance are not known.[66]

A recent study demonstrated that females are also more often likely to switch anti-TNF therapy than males; findings which are consistent with the rheumatology literature demonstrating that female patients with rheumatoid arthritis and spondyloarthritis switch anti-TNF therapy more often than males.[67,68] At least among patients with IBD, the reason for discontinuation was most often due to side effects.

Ustekinumab, a monoclonal antibody against IL-12/IL-23 approved for treatment of CD, was initially approved for psoriasis. While there are some data to support lower rates of sustained clinical response among males with psoriasis treated with ustekinumab compared with females, no data are yet available for IBD.[69]

One study of 86 pediatric patients with IBD who were treated with azathioprine alone and who had metabolites checked reported no differences in metabolite levels or response to therapy by sex.[70] One study of therapy de-escalation reported that, among patients with CD, male sex was associated with higher risk of relapse with withdrawal of azathioprine, a finding that is consistent among UC patients de-escalating immunomodulator therapy.[71–74]

Many studies demonstrate sex-based differences in *adherence to* therapy, which will certainly impact observed therapeutic response. Unfortunately, the body of literature is again heterogeneous with respect to study design and population, thus yielding mixed results, with some studies demonstrating female sex is associated with nonadherence,[75–77] while others demonstrate male sex is a risk factor.[78,79]

Further complicating our understanding of sex-based differences in therapeutic outcomes is confounding due to potential selection bias. A German multicenter retrospective cohort study of 986 patients with IBD found that females were treated with immunomodulatory medications less often and, relatedly, less often achieved disease remission compared with male counterparts.[80] This study was limited by a low number of patients receiving biologics, but the findings are notably congruent with data from a large US private-insurer claims database, where males were more likely to be treated with maintenance medications, including biologics, immunomodulators, and 5ASAs, compared with females ($p < 0.01$). The authors[81] also reported that females were more often treated with steroids and opiates, and males more often underwent IBD-related surgery. Unfortunately, individual-level data and more granular details are limited due to the nature of administrative-claims data.

Complications

Complications of IBD include both direct disease-related complications, such as fistulae, abscess, malignancy, and others, and therapy-related complications, such as infection, hematologic aberrancies, as well as malignancy. Indirect effects including the impact on quality of life and societal productivity are also of critical importance. While the literature is limited, there are some sex-based differences in IBD complications.

Male sex has been suggested associated with increased risk of complications of IBD.[82] In one cohort analysis of Israeli patients with CD who underwent genetic testing at baseline, researchers aimed to identify factors independently associated with CD complications, defined in the study as need for surgery, penetrating disease, strictures, or perianal disease. On multivariable analysis of patient clinical and genetic factors, only male sex was identified as an independent risk factor for complications; specifically, the need for surgery. Several studies corroborate the authors' findings, that is, males generally undergo more IBD-related surgeries compared with females, irrespective of CD *versus* UC,[11,83–86] although there are still some inconsistencies.[10,11]

Sex-based differences have also been observed in the postoperative period. One single-center retrospective study evaluated sex-based differences in peri- and postoperative outcomes.[87] While surgery type and pouch configuration were similar between the two groups, males more often than females needed an ileostomy and had an anastomotic leak within the first 30 days (3.8% *versus* 1.8%, $p < 0.01$). A recent multicenter study of 439 hospital admissions for IBD found that male sex was a risk factor for 1-year readmissions.[88] Over long-term follow up (median 9.3 years for males, 9.9 years for females), females more often experienced bowel obstruction, pouch-related fistula, and clinical symptoms, including bowel frequency and incontinence, and more often reported worse quality of life ($p < 0.05$ for all).

Pancreatitis is also associated with IBD, irrespective of whether the presumed etiology is related to thiopurine use or autoimmune pancreatitis. Based on a recent review, pancreatitis occurs more commonly in male patients with IBD.[89]

Bone health is an important part of maintenance care for IBD patients. A recent analysis of a nationwide inpatient sample found that female sex was associated with increased rates of hospitalization for fractures among patients with IBD.[90]

Some patients with colonic IBD are at increased risk of colorectal neoplasia. A recent meta-analysis of patients with IBD-associated colorectal cancer did not find significant differences in sex distribution when compared with sporadic colorectal cancer.[91] The use of some IBD therapies is associated with a very small, but still measurable, increased risk of certain malignancies. The use of thiopurines is associated with an increased risk of lymphoma, the most concerning of which is hepatosplenic T-cell lymphoma, especially in male patients.[92,93]

There are also differences in symptom and quality-of-life scores between males and females, independent of objective disease activity. One recent registry-based analysis demonstrated that, among patients with IBD, rheumatoid arthritis, or psoriasis, females more often reported worse symptoms for a given disease activity level compared with males, although the difference was not significant for the IBD subgroup.[94]

Conclusion

There are clear sex-based differences observed in IBD pathogenesis, epidemiology, clinical course,

and disease outcomes. There are varying levels of evidence suggesting that the complex interaction between well-described factors of pathogenesis, including genetic predisposition, immune dysregulation, environmental exposures and intestinal dysbiosis, might be modified by sex-dependent factors. Differences in incidence by sex and geography warrant further investigation and suggest there may be other mediating factors that have yet to be defined. In addition to these biologic factors, the impact of healthcare systems and differential access to care by sex on patient outcomes should not be underestimated. For instance, barriers to treatment with maintenance medications for female patients should be identified and addressed to improve patient outcomes. Further investigation on the impact of sex hormones on IBD is warranted and may result in better therapeutic response and disease course for our patients with IBD.

Author contributions

SR undertook the literature search and wrote the manuscript. MK and SS wrote and revised manuscript. All authors critically revised the manuscript and approved the final version.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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