Impact of Female Gender in Inflammatory Bowel Diseases

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Inflammatory bowel diseases show a gender bias, as reported for several other immune-mediated diseases. Female-specific differences influence disease presentation and activity, leading to a different progression between males and females. Women show a genetic predisposition to develop inflammatory bowel disease related to the X chromosome. Female hormone fluctuation influences gastrointestinal symptoms, pain perception, and the state of active disease at the time of conception could negatively affect the pregnancy. Women with inflammatory bowel disease report a worse quality of life, higher psychological distress, and reduced sexual activity than male patients.

inflammatory bowel disease | Crohn's disease | ulcerative colitis | female sex | female gender

1. IBD Medical Treatment

Several pharmacological and nutritional approaches are currently available to handle IBD, but their efficacy is still under evaluation because of the novelty of some of them [1][2]. However, clinical data show that IBD management and therapy differ between males and females. Females receive fewer IBD-specific treatments than males, while major abdominal surgery is performed more frequently in men than women [3][4][5][6]. A study on 986 outpatients reported that women received less immune-suppressive treatment despite their higher disease activity [4]. Many reasons may be advocated for this finding in men: (a) higher risk of developing severe disease; (b) lower compliance to corticosteroids and/or aminosalicylates; and probably (c) lower propensity to treat women of childbearing age with immunosuppressants [4]. These possible explanations were recently tested by a Canadian study in South-West Ontario [7], examining over 1000 IBD participants. The results demonstrated that women were more commonly treated with budesonide, while men were treated with prednisone, as also confirmed by Severs et al., 2018 [3]. Moreover, the use of immunomodulators is predominant in men vs. women (86.6% vs. 78.3%; p = 0.008), and, nevertheless, women were more prone to experience adverse drug reactions (29.5% vs. 21.2%; p = 0.01) [7]. The same study also found that age is predictive of biologics treatment in women, as those over 55 less frequently receive biologics. Overall, women responded better to treatment than men [8], but they displayed lower adherence to biological treatment [9]. On the other hand, males tolerate drug therapy better than females, who reported more prominent side effects. Studies assessing IBD clinical features and management are summarized in **Table 1**.

Table 1. IBD Clinical features and management.

Study	Study Population	Outcome
Wagtmans et al., 2001 [10].	541 CD patients (266 males, 275 females).	No difference in mean lag time between onset of symptoms and diagnosis, and no differences in presenting symptoms and initial localization of lesions. Similar percentage of patients who underwent an abdominal operation (81% vs. 77%). No difference in mean lag-time between onset of symptoms and first bowel resection. Lag-time between bowel resection and recurrence of disease shorter in women than in men (4.8 yr vs. 6.5 yr), ileocecal resections more frequent in female than male patients (44% and 32%, respectively). Female patients have significantly more often relatives in the first or second degree affected by CD than male (15% vs. 8.3%).
Severs et al., 2018 [3].	Dutch IBD Biobank study: 2118 CD and 1269 UC patients. COIN study: 1139 CD and 1213 UC patients.	Early onset CD (<16 years) more frequent in males than in females (20% vs. 12%). Male CDs have more often ileal disease (28% vs. 20%) and underwent more often small bowel and ileocecal resection. Male CDs used prednisone more often and suffered more often from osteopenia. IBD-specific healthcare costs did not differ between male and female IBD patients. Extraintestinal manifestations more frequent in female IBD patients than male.
Mazor et al., 2011 [11].	146 patients with CD (76 females, 70 males) treated during a 10-year period.	The only independent risk factors associated with developing a complication were smoking and male gender. There was no association between developing complications and the presence of selected SNPs (p = 0.07 for tyrosine residue on both alleles in NCF4 SNP rs4821544 and p = 0.06 for a guanine residue on both alleles in ATG16L SNP rs2241880). Multivariate analysis using a backwards logistic regression model left only male gender as an independent statistically significant association with complicated disease (OR 2.6017, 95% CI: 1.17 to 5.75). The median time to developing a complication was 4 years, and the most common complication was the need for surgical intervention (54%).
Blumenstein et al., 2011 [4].	986 patients with IBD (515 CD, 471 UC—537 females, 449 males).	Extended disease duration in women, no significant gender-related differences in demographic and clinical characteristics observed. Men showed a significantly higher remission rate than women (p = 0.025), while women received significantly less immunosuppressive medication compared to men (p = 0.011). Treatment with immunosuppressants was not different in women with child-bearing potential compared to menopausal women.
Bokemeyer et al., 2013 [12].	1032 patients with IBD (511 CD, 519 UC, 2 IBD-U).	About one third of the IBD patients were not in clinical remission (CDAI ≥ 150/CAI > 4) (CD: 45%; UC: 27%), although high rates of immunosuppressive drugs (CD: 47%; UC 26%) were administered. This study shows a large burden of active disease associated with an unexpectedly high (co)morbidity and high psychosocial impairments, indicating a reduced health state in IBD patients.

Study	Study Population	Outcome
Greuter et al., 2018 [13].	1638 CD patients (107 presented with upper GI tract involvement at the time of diagnosis, 214 at any time).	In a multivariate logistic regression model, male sex, and diagnosis between 2009 and 2016 (versus before 1995) were independent predictors for presence of upper GI tract involvement at CD diagnosis (odds ratio [OR] 1.600, $p = 0.021$ and OR 2.686, $p < 0.001$, respectively), whereas adult age was a negative predictor (OR 0.388, $p = 0.001$). Patients with upper GI tract involvement showed a disease course similar to control patients (hazard ratio [HR] for any complications 0.887, (95% confidence interval [CI] 0.409–1.920), and a trend towards occurrence of fewer intestinal fistulas (log-rank test $p = 0.054$).
Jussila et al., 2014 [14].	21,964 patients with IBD (5315 CD, 16,649 UC).	Overall mortality was increased among patients with CD (standardized mortality ratio (SMR) 1.33, 95% confidence interval 1.21–1.46) and UC (1.10, 1.05–1.15). SMR was significantly increased for gastrointestinal causes in CD (6.53, 4.91–8.52) and UC (2.81, 2.32–3.34). Patients with UC were found also to have increased SMR from pulmonary (1.24, 1.02–1.46) and cardiovascular disease (1.14, 1.06–1.22) and cancers of the colon (1.90, 1.38–2.55), rectum (1.79, 1.14–2.69) and biliary tract (5.65, 3.54–8.54), whereas SMR from alcohol-related deaths was decreased (0.54, 0.39–0.71). Patients with CD had a significantly increased SMR for pulmonary diseases (2.01, 1.39–2.80), infections (4.27, 2.13–7.63) and cancers of the biliary tract (4.51, 1.23–11.5) and lymphoid and hematopoietic tissue (2.95, 1.85–4.45).
Peyrin-Biroulet et al., 2013 [5].	310 patients with CD (154 females, 156 males).	The cumulative probability of major abdominal surgery was 38, 48, and 58% at 5, 10, and 20 years after diagnosis, respectively. Baseline factors significantly associated with time to major abdominal surgery were: ileocolonic (hazards ratios (HRs) 3.3), small bowel (HR, 3.4), and upper gastrointestinal (HR, 4.0) extent, relative to colonic alone; current cigarette smoking (HR, 1.7), male gender (HR, 1.6), penetrating disease behavior (HR, 2.7), and early corticosteroid use (HR = 1.6). Major abdominal surgery rates remained stable, with 5-year cumulative probabilities in 1970–1974 and 2000–2004 of 37.5 and 35.1%, respectively. The cumulative probability of major abdominal surgery in this population-based cohort of Crohn's disease approached 60% after 20 years of disease, and many patients required second or third surgeries. Non-colonic disease extent, current smoking, male gender, penetrating disease behavior, and early steroid use were significantly associated with major abdominal surgery.
Walldorf et al., 2013 [15].	293 patients with IBD (195 CD, 98 UC—110 males, 183 females).	DEXA-scan was performed in 174 patients (59 males, 115 females). Bone mineral density (BMD) was impaired in 38.5% of these patients. Male patients were diagnosed more often with osteopenia or osteoporosis than females (55.9% vs. 29.6%, $p = 0.03$) and had a risk of bone disease comparable to postmenopausal women. Additionally, duration of corticosteroid treatment and IBD were identified as risk factors for osteoporosis. Follow up DEXA-scan demonstrated an overall deterioration of BMD in patients with normal baseline results.
Sigurdsson et al., 2022	49 young adult male patients	The group of young adult patients had, in comparison with the controls, significantly smaller median cortical area (126.1 mm^2 vs 151.1 mm^2, $p <$

Study	Study Population	Outcome
[16].	with childhood-onset IBD and 245 matched controls.	0.001), lower median total vBMD (296.7 mg/cm^3 vs. 336.7 mg/cm^3, p < 0.001), and lower median cortical vBMD (854.4 mg/cm^3 vs. 878.5 mg/cm^3, p < 0.001). Furthermore, the patients compared with the controls had lower median trabecular volume fraction (16.8% vs. 18.2%, p < 0.001) and thinner median trabeculae (0.084 mm vs. 0.089 mm, p < 0.001). The differences between the patients with IBD and controls persisted in multivariable analyses that included adjustments for SMI and physical exercise.
[17]		
Heath et al., 2022 [7].	1015 patients; 656 CD (59.0% women) and 359 UC (47.9% women).	Women were more likely prescribed budesonide than men (23.6% vs. 13.4%; p < 0.0001), more men were exposed to prednisone for IBD management (73.5% vs. 67.4%; p = 0.04). Immunomodulator use was higher in men with CD versus women (86.6% vs. 78.3%; p = 0.008) and of those exposed, women more commonly experienced ADRs (29.5% vs. 21.2%; p = 0.01). Though no sex-related difference was identified, age was a predictor of biologic exposure in women with CD and men with UC, with those > 55 being less likely to receive biologics.

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tercourse which are rtility rate astomosis vels as a between owever, a men with physiological ovarian reserve (matched by age) concluded that hormone levels were significantly lower in ≥30-year-old women with colonic CD involvement compared to the controls [23]. Moreover, AMH levels were lower in active disease and inversely correlated with the Crohn's Disease Activity Index, suggesting that the active disease may compromise fertility [24][25][26].

Although evidence indicated no differences in fertility rates between IBD and healthy women, patients showed half the number of children vs. healthy women, a feature known as "voluntary childlessness" [22]. This lifestyle may be explained by both mechanical and psychological grounds. From a mechanical point of view, surgical interventions greatly affect women's anatomy, significantly reducing their ability to conceive. UC women undergoing deep pelvic dissection show a higher risk of pelvic adhesions, formation of scar tissue, post-operative dyspareunia, tubal obstruction, or alteration of the tubal-ovarian crosstalk, causing a threefold reduction in the fertility rate [27][28]. A systematic meta-analysis on the relative risk of infertility post-ileal pouch-anal anastomosis in women with UC showed that infertility increased from 15% to 48% [29]. In agreement with this result, a systematic literature search considering 22 studies reported increased infertility from 12% before restorative procto-colectomy to 26% after the intervention [27]. Moreover, a retrospective study investigating seventy-one women who had undergone procto-colectomy and ileostomy for UC and CD reported a reduction from 72% to 37% in fertility after surgery [30]. On the other hand, the psychological reluctance to conceive may depend on an altered perception of reality, which leads to an unjustified fear of the hereditary transmission of IBD, congenital abnormalities, pregnancy risks, worsening of the IBD condition during the pregnancy, and medication teratogenicity [31]. Regarding IBD heritability, available data suggest only a partial influence of the genetic components on disease onset, with high chances that the child will not develop the disease (91% if only one parent is affected and 60% if both parents are affected).

3. Pregnancy

Studies on IBD and pregnancy are contradictory. Some evidence suggests that conception occurring during the phase of active disease leads to a relapse of the illness in 2/3 of patients, with symptoms worsening in more than 60% of cases [32]. Moreover, the state of active disease at the time of conception could negatively affect the fetus, increasing the risk of miscarriage and reducing birth weight and pre-term birth [33]. Conversely, some studies have described a positive effect of pregnancy on IBD symptoms, especially when gestation starts during a period of disease remission. The gestation effects on IBD pathology are reported to be positive also when pregnancy starts during active disease, leading to remission in more than 70% of women with CD and more than 65% of women with UC [17][31][33]. Indeed, the intensification of symptoms during pregnancy is only transitory, and it appears during the first trimester, mainly provoked by the discontinuation of the maintenance therapy.

With regard to the worsening of the IBD condition, women conceiving during illness remission have the same chance of exacerbation as non-pregnant patients with IBD [17][31][33][34]. Pregnancy-induced positive effects are long-term, influencing the disease symptoms over a period that may last years. Available data show a reduction in the rates of stenosis and resection and annual exacerbation rates (from 0.34 to 0.18 in UC and from 0.76 to 0.12 in CD) [33][35]. The reasons underlying these findings remain elusive, but they could be associated with the positive effect of pregnancy on the immune system and the beneficial role that sex hormones exert on IBD symptoms.

Indeed, studies in animal models showed that the progressive increase of estrogen and progesterone throughout gestation decreased pro-inflammatory cytokine production and improved intestinal epithelial barrier function, reducing bacterial translocation and IBD activity at the end of pregnancy [18][36]. Despite concerns about continuing drug medication during pregnancy and breastfeeding, data indicate that, except for methotrexate, drugs used for IBD treatment are generally safe and do not increase the risk of congenital abnormalities or adverse effects on the fetus. The Toronto and ECCO consensus statements recommend continuing thiopurines, or anti-TNF alpha agent therapies during pregnancy in well-controlled women, as the treatment benefits outweigh the risks.

There is still much confusion about the effect that IBD could have on pregnancy; therefore, it is of paramount importance that women affected with IBD and with the desire to conceive be addressed by proper medical counseling [17]. Compliance with treatment improves in women who receive an appropriate consultation regarding drug therapy before conception and during gestation [33][37]. Thus, gastroenterologists should stimulate discussion about concerns related to IBD and pregnancy, reassuring patients about treatment safety. Overall, the importance of maintaining disease remission should be emphasized for the best pregnancy outcome.

4. IBD and Female Hormones

Fluctuation in ovarian hormone levels influences visceral hypersensitivity, GI transit time (via sex hormone receptors), and pain perception (via opioidergic and serotonergic systems) [38][39]. Puberty, pregnancy, and menopause are the three phases in a woman's life in which sex hormones have a crucial role and influence IBD symptoms and outcomes [40]. Hormones, such as 17-beta estradiol (estrogen), prolactin, and testosterone, are considered directly involved in symptom variation, albeit molecular and cellular mechanisms involved in IBD

pathogenesis are still poorly understood. Moreover, the activation of estrogen receptors expressed by epithelial cells contributes to the increase of gut permeability and the activation of humoral and cellular immunity [38].

Notably, the estrogen receptor beta (ERb) seems to have a role of paramount importance in IBD. The ERb is highly expressed in colonic epithelial cells, thereby preserving tight-junction organization, mucosal structure, and barrier function. Interestingly, its expression is markedly reduced in the colonic mucosa of CD/UC patients with active disease [41]. Upon ligand binding, ERb translocates into the nucleus and regulates the transcription of target genes [40]. In an experimental model of CD-like ileitis, Goodman et al. found that ERb protected male but not female mice. Conversely, ERb activation was associated with an anti-inflammatory effect in female but not in male UC models. The molecular mechanisms underlying ERb signaling, and, in general, intestinal inflammation may explain the gender gap observed in the UC incidence, as seen in CD [42].

The different phases of the menstrual period affect GI symptoms cyclically, and menstruation worsens GI symptoms, primarily diarrhea, in IBD women. Indeed, studies investigating the effect of IBD disease activity and medications on GI symptoms during the menstrual cycle found a correlation between disease activity and the worsening of GI symptoms [43]. Consequently, treatment of menstrual disorders with non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraceptive pills (OCP) may influence the IBD course. Women affected by IBD showed a delayed onset of puberty and irregularities in menstrual function (e.g., menstrual abnormalities, oligomenorrhea, and polymenorrhea) [38][44]. Interestingly, alterations in the menstrual cycle can occur a year before IBD diagnosis and are favored by corticosteroids [45]. The mechanisms that evoke menstrual cycle abnormalities are yet to be clarified; possibly, the stress associated with a chronic disease, surgeries, and nutrient malabsorption could play a role. Surprisingly, symptoms improved with the increase in disease duration. Studies on the contribution of menopause and hormone replacement therapy (HRT) on IBD disease activity are few and inconsistent. Some evidence suggested that CD could anticipate menopause [46], while others found no differences between IBD women and healthy controls [47]. Thus, menopause has little or no effect on disease activity and flares.

Research evaluating the association between IBD and HRT found a decrease in the risk of flares during the first two years after menopause, a phenomenon likely promoted by the anti-estrogen action known to exert inflammatory properties [48]. Conversely, a study on American women found a correlation between the use of HRT and the risk of developing UC, but not CD [49]. HRT-UC relation could be allegedly induced by the effect of estrogens on intestinal permeability, immune function, and influence on gut microbiota.

Few studies have also investigated the role of OCP on IBD flare-ups. One study of 152 CD patients reported an increased risk of relapse among CD patients taking OCP [50]. In contrast, another study of 331 women aged 16–50 found no increase in the risk of relapse in patients with CD on OCP treatment [51]. In this subset, it has been speculated that the increased risk of CD in patients may be due to the effect of estrogen on venous hypercoagulability. In addition, estrogen may enhance the development of T helper 1 (Th1) and/or T helper 2 (Th2)-mediated inflammatory diseases. Finally, the modification of the gut microbiome should be addressed. The

increased risk of CD in premenopausal women on OCP and the risk of increased UC in postmenopausal women on HRT could explain the differences in the hormonal milieu during each state [52].

5. IBD and Female Psychology

Psychiatric disorders and psychological distress showed a female preponderance in IBD. Self-reported quality of life questionnaires showed lower scores in females than in males [53][54][55]. A Chinese study involving more than 1000 participants of both genders suggests that the impact of CD in females is related to a lower satisfaction level of quality of care (QoC) due to disease symptoms (e.g., pain and discomfort) and depression [56]. Another study aimed at finding gender-specific concerns in 1102 Swiss IBD patients revealed that cancer risk is the primary concern for both genders. Women >40 years old were not worried about their illness but being unemployed increased their concern [57]. Fatigue, a typical symptom of IBD, seems to be more present in women than men, independently from anemia and the state of activity of the disease [58][59][60][61]. Moreover, sexual activity is reduced in women more than men, mainly because of their impaired sexual body image and libido after surgery [62][63]. However, although females appear to be more prone to psychological disorders, they are also interested in receiving information regarding depression from specialists and media [64]. Additionally, when the disease is active, women report more use of emotion-focused and problem-focused coping than men. Such behavior may depend on the traditional role of family caregivers, which is still strongly present in developed countries. In general, society has always invested women with a clear system of expectations that has distorted the real perception of their nature. However, in recent years, scientific research has begun to investigate women with a more rational and objective approach. In this light, there is a need for future studies that will accompany women's methods of coping with various diseases in a way that "exceeds" or counters the "normative" set of expectations that has been adapted to the male methods of recovery and coping [65][66].

Studies evaluating psychosocial distress, emotional disturbances and impaired QoL in patients with IBD are summarized in **Table 2**.

Table 2. Studies evaluating psychosocial distress, emotional disturbances and impaired QoL in patients with IBD.

Study	Study Population	Outcome
Nurmi et al., 2013 [53].	556 patients with IBD (292 females, 264 males).	Women had seen doctors more often than men ($p < 0.001$). Women were absent from work more frequently than men ($p = 0.01$). The amount of physician visits, work absenteeism, and a higher amount of undergone procedures were related to impaired HRQoL ($p < 0.001$ on all accounts).
Graff et al., 2006 [54].	388 patients with IBD.	Multivariate regression showed that those with active disease had higher levels of distress, health anxiety, and perceived stress, lower social support, well-being and mastery, and poorer disease-specific QOL, relative to those with inactive disease. Participants with either active or inactive disease had suboptimal general QOL.
Hauser et al., 2011	112 IBD patients (51 CD, 61 UC—50	Women have expressed significantly lower level of the general HRQoL and more emotional disturbances connected with their disease as well as

Study	Study Population	Outcome
[55].	females, 62 males).	more frequent bowel symptoms compared with men.
Yan et al., 2020 [56].	891 IBD patients (522 CD, 363 UC, 6 IBD-U—362 females, 529 males).	Female patients showed a higher tendency to feel that the quality of communication with specialists (p = 0.037) and quality of IBD care (p = 0.019) was less satisfactory than male patients. Female patients with IBD show a larger number of intense concerns, a greater level of psychological disturbance, a higher symptom load, and a poorer QoL than men, resulting in reduced satisfaction ratings.
Pittet et al., 2017 [57].	1102 IBD patients (596 CD, 475 UC, 31 IBD-U—598 females, 504 males).	Women had significantly higher overall levels of concern than did men (sum score: 47.5 vs. 42.8, respectively, $p < 0.001$). Women at home or unemployed had higher concerns about disease-related constraints and uncertainty (p = 0.004). Patients seem to have important gender-specific concerns related to their illness.
Saraiva et al., 2019 [58].	105 IBD patients (60 CD, 45 UC—60 females, 45 males).	Female gender and active CD were significantly associated with a severe level of fatigue (p = 0.05 and p = 0.04).
Bager et al., 2012 [59].	425 IBD patients (251 CD, 174 UC).	Female IBD patients tend to experience more fatigue than males. When comparing the IBD patients with disease activity to the IBD patients in remission, all dimensions of fatigue were statistically significant (p <0.05). Fatigue in IBD is common regardless of anaemia or iron deficiency. Fatigue in IBD is most marked for patients <60 years of age. Fatigue is expressed differently between groups.
Le Berre et al., 2019 [60].	1410 IBD patients (875 CD, 496 UC, 39 IBD-U).	Among the disabling symptoms at work, fatigue was the most frequent (41%) followed by diarrhea (25%) and fecal incontinence (18%). IBD has a strong negative impact on working life. While work satisfaction remains high, IBD affects career plans.

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