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Review Article

Unique Considerations in Women with Inflammatory Bowel Disease

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Abstract

The incidence of Inflammatory Bowel Disease (IBD) is increasing globally. Female patients have special considerations such as hormonal fluctuations affecting gastrointestinal symptoms; Oral Contraceptive Pill (OCP) use and effects on IBD development, need for surgery, Venous Thromboembolism (VTE) risk; fertility; and cervical cancer screening. Providers must be aware of these important considerations in female patients, and this review seeks to delineate these important, non-pregnancy related issues.

Epidemiology

Inflammatory Bowel Disease (IBD) is a chronic gastrointestinal inflammatory disease that includes both Crohn's Disease (CD) and Ulcerative Colitis (UC). The epidemiology of IBD continues to change globally and the rates of IBD have increased with time [1]. The incidence of IBD has increased in developing countries as these regions become more westernized [2]. The cause for this is unclear, however many have hypothesized that sanitation, diet, microbial exposure, and pollution may be involved [2].

A population-based cohort study of Olmsted County, MN residents from 1970-2010 showed the incidence rates for men compared to women are consistently higher across all age groups [3]. There is a divergence at older ages and the reason for this is unclear [3]. On the other hand, the incidence rates of CD is similar in men and women[3]. However, the data have been divergent on rates of CD between males and females. For instance, other studies have found in Europe and the United States, CD prevalence may be higher in females than males[4]. Early-onset CD has been found more frequently in males than in females; older females (ages 25-29 and more so in those over the age of 35) have been more likely to develop CD compared to males [4]. One study estimated a risk of up to 40% [4]. Betteridge, et al. assessed the prevalence of IBD in a military health care population between 2008-2009 and found that IBD was more prevalent in females compared to males (Relative Risk [RR] 1.53; 95% confidence interval (CI), 1.50-1.57) [5,6]. Additionally there was an increased prevalence of IBD seen at older ages.

Hormonal Fluctuations & IBD Symptoms

Women with IBD may report either improved or worsening gastrointestinal symptoms during their menstrual cycle. Rolston, et al. studied the association between hormonal fluctuations and change in IBD symptoms in an online cohort of women using a 5-point Likert scale [7]. Over half of the women in this study had increased symptoms during their menses and there was no significant difference between women with CD and UC [7]. About 30% of this cohort did report extreme change in symptoms at time of hormonal fluctuations [7]. In this study use of HRT and hormonal contraception was not associated with change in IBD symptoms [7]. There was no significant change in IBD symptoms after menopause [7]. Also, interestingly, pregnancy was associated with an improvement in symptoms in a majority of female patients with IBD.

However, the data in the literature about symptom change during menstruation has been variable. Some studies have found higher rates of diarrhea during menses in women with CD than in those with UC, and women with CD were more likely to report worsening symptoms than those with UC [8-10]. There have been a number of proposed mechanisms by which hormonal fluctuation could affect the gastrointestinal tract: prostaglandin production and

its effect on colonic smooth muscle and estrogen's effects on gut permeability and motility [7]. However, it is unclear if symptom increase during hormonal fluctuations translates to an increase in IBD-related inflammation [7]. Therefore, if there is an increase in gastrointestinal symptoms, increased inflammatory activity must be confirmed with objective biomarkers or endoscopic/radiographic evaluation before appropriate therapy can be instituted.

Oral Contraceptive Use and IBD

Oral contraceptive pills (OCP) are commonly used for contraception. There have been differing data on the relationship between OCP use and the development of IBD. A meta-analysis was completed in 2017 to assess the association between OCP use and risk of IBD [11]. Ortizo, et al. found an increased risk of IBD development in patients exposed to OCP compared to those who were not exposed to these medications (odds ratio [OR]: 1.32, 95% CI: 1.17-1.49, $p<0.001$) [11]. This study found a 24% increased risk of developing CD and a 30% increased risk of developing UC in those exposed to OCP [11]. However, further studies are needed to elucidate the total dose and duration of OCP use and its effect on development of IBD.

Long-term use of OCP may be associated with increased risk of surgery [12]. A prospective study of female CD patients from the Swedish National Patient Register studied this with the primary outcome of interest being first CD-related surgery [12]. They found a higher risk of surgery in current OCP users compared to non-OCP users; the risk of surgery increased with longer term use of OCP[12]. OCP use and active IBD may increase the risk of VTE. The overall risk of VTE in IBD patients is higher than in those without IBD (Hazard Ratio [HR] 3.4, 95% CI 2.7-4.3, $p<0.0001$) [13]. Furthermore, the risk of VTE in an IBD patient who is experiencing a flare is significantly higher (HR 8.4, 95% CI 5.5-12.8, $p<0.0001$) [13]. The risk for VTE in the general population is higher in those with OCP use compared to those without OCP use [14]. Pellino, et al. conducted a retrospective review of an Italian IBD database and compared 146 IBD patients on OCP to 290 non-IBD matched controls [15]. They found no significant difference in the incidence of VTE between IBD patients in remission and in non-IBD patients [15]. In general, there is likely little avoidance of estrogen-based contraception in usual clinical practice [16,17]. However, it may be prudent to avoid estrogen-based oral contraceptives in those with multiple VTE risk factors such as active uncontrolled IBD, current smoking, and history of VTE.

Fertility and IBD

Since IBD can affect women of childbearing age, fertility can be a significant issue. Voluntary childlessness is more commonly noted in patients with IBD than in the non-IBD population [18]. Studies have suggested decreased fertility in women with active CD but normal fertility in women with CD in remission and in women with UC [19-21]. Decreased fertility may be related to transmural inflammation leading to pelvic inflammation, which in turn could affect the ovaries and fallopian tubes, and a decrease in anti-Mullerian hormone [22]. Studies of women with UC who undergo total proctocolectomy with Ileal Pouch Anal Anastomosis (IPAA) have shown a threefold increase in infertility (average infertility rate increased from 15% to 48% post IPAA) [23]. However, the success rates of *In Vitro* Fertilization (IVF) in women with IPAA are similar to women with UC without an IPAA and to non-IBD patients [24].

A population-based study from Sweden conducted by Druvefors, et al. showed that fertility was decreased in women with CD but was almost normal in women with UC [22]. Increased disease severity and number of surgeries was associated with decreased fertility [22]. Active disease and flares may decrease fertility by local inflammation on pelvic organs, malnutrition, and associated depression [22]. Therefore, aggressive treatment to prevent severe, complicated disease requiring surgeries is paramount, and a multidisciplinary approach is the most effective.

Cervical Cancer Screening

Health maintenance is an extremely important aspect of the care of patients with IBD. Risk factors associated with increased risk of cervical cancer include smoking and immunosuppression [25]. Some data suggest that women on immunosuppression, such as IBD patients on biologics, thiopurines, or methotrexate, are screened less frequently than what is recommended [25]. Singh et al. conducted a study that showed 54% of women with IBD received cervical cancer screening, however exposure to immunosuppression and having a diagnosis of CD were independent predictors of decreased screening [26]. A meta-analysis by Allegretti, et al. found that there may be an increased risk of cervical high-grade dysplasia and cancer in IBD patients who are on immunosuppression [27]. Given this, the recommendation for cervical cancer screening in IBD patients by the American College of Gastroenterology (ACG) states that "women with IBD on immunosuppressive therapy should undergo annual cervical cancer screening [25]." Notably, both the American College of Obstetricians and Gynecologists (ACOG) and the Centers for Disease Control (CDC) also suggest annual screening for women who are chronically immunosuppressed [25].

Conclusion

There are several issues that are unique to women in the medical management of IBD. Hormonal fluctuations may affect gastrointestinal symptoms however it is unclear if this translates to increased disease activity. OCP may be implicated in the development of IBD and there may be an association with CD-related surgeries. However, it is important to be cautious of OCP use in IBD patients who have multiple VTE risk factors. The data is

variable on fertility rates in women with IBD but there is a decrease in fertility rates in those who have undergone an IPAA procedure. Finally, it is important to remember cervical cancer screening in IBD patients especially those who are immunosuppressed. Providers must be cognizant of these special issues when seeing women with IBD.

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