ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Sexual Issues and Fertility in Male Patients With Inflammatory Bowel Disease

Muhammad B. Hammami, MD
Assistant Professor of Medicine
Loma Linda University School of Medicine
Health Sciences Assistant Clinical Professor
University of California Riverside School of Medicine
Division of Gastroenterology and Hepatology
VA Loma Linda Healthcare System
Loma Linda, California

G&H What have studies shown regarding the association of inflammatory bowel disease and male sexual function?

MH The impact of inflammatory bowel disease (IBD) on sexual function and interpersonal relationships has not been well defined due to scarcity of research in this area and the heterogeneity of the disease. However, it has been estimated that 15% to 25% of male IBD patients experience sexual dysfunction, as opposed to only 5% of men in the general population. In older German studies, over 40% of male patients with IBD reported severe sexual compromise in a survey of 280 patients, and approximately 33% of male patients in another study reported worsening of their sexual desire and satisfaction after being diagnosed with IBD. In a more recent nationwide Danish cohort study, prescriptions for erectile dysfunction were more likely to be filled by men with IBD than men without IBD. A meta-analysis of 7 studies, which included 351,668 male individuals, found that IBD was significantly associated with an elevated risk of sexual dysfunction in men (relative risk, 1.41; 95% CI, 1.09-1.81; P=.008; heterogeneity I^2, 80.2%; P<.001). In a meta-analysis of 5 studies, which consisted of 637 cases and 389 comparators, male patients with IBD had significantly lower scores in sexual function indexes, with a pooled mean difference of -3.8 (95% CI, -6.86 to -0.75; I^2, 53%).

G&H Why may IBD impact male sexuality?

MH IBD is diagnosed most often when men are in their 20s to 40s, which are the peak years of reproduction as well as the time when their sexual identity and relationships are developing. IBD likely has a negative impact on sexuality due to its chronic relapsing course, erratic and unpredictable symptoms, and invasive surgeries. All of these factors can result in significant morbidity, as well as impaired quality of life, body image, mood, and fatigue, and can ultimately impact one's sexual function.

G&H What factors have been associated with sexual dysfunction in male patients with IBD?

MH An IBD-specific questionnaire that measures sexual function identified depression, increased disease activity, and a history of ileoanal pouch–anal anastomosis (IPAA) as being associated with sexual dysfunction in male patients with IBD. Other studies have identified additional factors, including medications; nutritional deficiencies; hypogonadism; invasive abdominal, pelvic, and perianal surgical treatments; tobacco use; older age; and psychological disorders.

G&H What have studies found regarding the relationship between IBD surgery and male sexual dysfunction?

MH Despite improvements and the expansion of medical treatment for patients with IBD, surgery remains a common part of the experience of having IBD. Although there have been several studies looking at the relationship between IBD surgery and sexual dysfunction, much of this research has been retrospective in nature, and none has involved controlled trials. Most of the studies have involved patients with ulcerative colitis, with the most common surgeries being proctocolectomy and IPAA. Sexual dysfunction after undergoing proctocolectomy may be caused by nerve damage, changes in anatomy, fibrosis, or psychological issues. After this procedure, erectile dysfunction occurs in 0% to 26% of patients. Interestingly, converting a traditional ileostomy to a continent ileostomy was associated with an improved quality of sexual life, and undergoing proctocolectomy with IPAA was associated with less restriction on sexual activity compared to undergoing a continent ileostomy or a traditional ileostomy. This raises the suggestion that body image may impact sexual function in addition to, and independent of, pelvic innervation damage.

Sexual dysfunction may decrease when disease activity is controlled, nutrition (such as sufficient flavonoid) is improved, alcohol and tobacco use are discontinued, and mental health is managed.

G&H Have studies shown an association between disease activity and male sexual dysfunction?

MH Older studies have not consistently demonstrated an association, unlike newer studies. The aforementioned study with an IBD-specific sexual function questionnaire found that disease activity was a significant factor. A higher rate of erectile dysfunction has been reported in male patients with IBD who have active disease than in healthy controls or in male patients with IBD that is in remission. Another study found that male patients with IBD who had active disease had significantly worse mean scores on the Arizona Sexual Experience Scale; 64% of these patients experienced sexual dysfunction.

Furthermore, other studies have shown that proinflammatory cytokines and reactive oxygen species in the setting of active inflammatory disease appear to negatively impact male sexual function. Other factors that have been shown to play a role in sexual dysfunction include deficient health and nutrition, IBD symptoms that are unpredictable, and depression, all of which are often associated with disease that is active.

G&H Have any IBD medications been shown to cause male sexual dysfunction? Should any treatment adjustments be made?

MH There have not been any studies on the relationship between IBD drugs and sexual dysfunction in male patients with IBD. Overall, none of the medications appear to contribute to sexual dysfunction, and adjustments should not be made unless the drugs have been identified as the cause. That being said, a handful of case reports have been published on this issue. Several case reports of patients with rheumatoid arthritis have suggested that impotence is associated with the use of methotrexate, while one case report of an ulcerative colitis patient noted that impotence was associated with the use of sulfasalazine. In addition, a case report of a rheumatoid arthritis patient noted the association of ischemic priapism with the use of adalimumab. In addition, several non-IBD medications that are often used in IBD patients, such as opioids, antidepressants, and anxiolytics, have been strongly associated with sexual dysfunction.

G&H How can sexual dysfunction best be managed in male patients with IBD?

MH Identifying the problem is the first step. Physicians, particularly gastroenterologists, should be vigilant that sexual dysfunction may occur, especially in at-risk patients. Sexual dysfunction may decrease when disease activity is controlled, nutrition (such as sufficient flavonoid) is improved, alcohol and tobacco use are discontinued, and mental health is managed. If sexual dysfunction is suspected, physicians should screen for low levels of testosterone, as they may contribute to the problem. Following IPAA, sexual dysfunction is not common in male patients with ulcerative colitis, but if it occurs, it can be managed with sildenafil. Seventy-nine percent and 17% of patients responded to treatment with sildenafil and placebo, respectively, in a randomized placebo-controlled trial of 32 male patients with erectile dysfunction following rectal excision for cancer or IBD. In addition, sexual function and disease activity may be improved with

the management of psychological conditions. One study found that the use of antidepressants for 6 months was associated with enhancements in quality of life, sexual functioning scores, depression, and anxiety.

G&H How common are infertility and voluntary childlessness in men with IBD?

MH A study of male Crohn's disease patients and age-matched controls found that Crohn's disease was associated with decreased birth rates. A survey of 255 IBD patients (of whom only 87 were male) found that over 40% of patients feared being infertile, in contrast to nearly 10% of the general population. However, more importantly, a doctor was consulted by only 19% for fertility issues. Voluntary childlessness, not infertility, may contribute to the low rates of birth. Male patients with Crohn's disease reported an increase in the risk of infertility of up to 50% without a change in their capacity for reproduction, which may suggest voluntary childlessness. One study has suggested that this may be due to various factors, including concerns of congenital abnormalities, the possibility of passing on disease, and the potential teratogenicity of IBD drugs.

G&H What has research shown regarding the possible effect of IBD medications on male fertility?

MH The only IBD-specific medication consistently shown to cause infertility is sulfasalazine. The first case report was in 1979. A few more recent studies have found that there is a nondose-dependent, nonuniversal, reversible toxic effect on spermatozoa and male fertility. Reduced sperm concentration was associated with the use of endogenous steroids in men who had undergone endurance training. However, no association was noted between the use of corticosteroids and infertility in patients with Crohn's disease, and semen quality was not negatively affected by adding corticosteroids to thiopurines. Animal research has shown that the use of methotrexate can degenerate cells (Sertoli, Leydig, spermatocytes). One case report in the dermatology literature has noted reversible methotrexate-associated oligospermia and another has reported irreversible methotrexate-associated oligospermia. However, a review of almost 50 men from 5 studies who were exposed to the drug did not find a negative effect on spermatogenesis.

In animal reproduction studies, tofacitinib (Xeljanz, Pfizer), the only Janus kinase (JAK) inhibitor that has been approved so far for IBD, has demonstrated adverse embryo-fetal findings and may reduce fertility in females (at doses higher than the recommended maximum dose); however, it is not known whether this applies to males. Human data on this issue are lacking. A study is currently underway on semen parameters and the selective JAK1 inhibitor filgotinib; however, no data are available yet. In contrast, patients with rheumatologic disorders have experienced improvements in semen parameters that were associated with better control of inflammation with the use of anti–tumor necrosis factor (TNF) agents. Finally, there are reassuring data on 5-aminosalicylate compounds as well as thiopurines, and limited data on biologics that are not anti-TNF agents, but they all appear to be compatible with use in male IBD patients who want to have children.

… there are reassuring data on 5-aminosalicylate compounds as well as thiopurines, and limited data on biologics that are not anti-TNF agents, but they all appear to be compatible with use in male IBD patients who want to have children.

G&H Are there any recommendations for men with IBD who want to have children or who are having trouble having children?

MH The path to investigating fertility in IBD patients involves considering IBD-associated causes and identifying at-risk patients early on. A comprehensive assessment should be undertaken, and medication use should balance disease control. Sulfasalazine should be switched to a 5-aminosalicylate compound. Patients who have difficulty conceiving should have their disease objectively staged with endoscopy, imaging, and/or serologic or stool inflammatory markers. In my opinion, it is key to achieve and maintain corticosteroid-free remission, withdraw corticosteroids once possible, evaluate the patient's nutrition, screen for zinc deficiency, and replenish any deficiencies. It is also important to screen for and treat

depression and hypogonadism, as well as discontinue any possible offending medications. Finally, early investigation and working closely with a reproductive endocrinologist should be encouraged.

G&H What is the role of the gastroenterologist in diagnosing and managing sexual dysfunction and fertility issues in male IBD patients?

MH The care of IBD patients starts with, and is led by, the gastroenterologist. The majority of IBD patients are diagnosed at a younger age, and their gastroenterologist is often their primary point of medical care and functions as their primary care provider. One study showed that only one-quarter of male IBD patients would like to talk to a doctor about their sexuality and that only approximately 40% of those patients do. Addressing sexual health should be part of the routine health maintenance assessment undertaken by the patient's provider. Some gastroenterologists believe that sexual health is unrelated to their field and, therefore, out of the scope of their practice. However, it is an issue that can easily be identified and, in most cases, managed either by gastroenterologists or through referral. Sexual health has important consequences for patients and their families, so more attention should be given to this area both clinically and academically.

G&H What are the next steps in research?

MH The next step is to design studies that explore the causes, prevention, and treatment of sexual dysfunction and infertility in IBD patients. Now that there are validated scales for the evaluation of sexual dysfunction in IBD, they need to be implemented in clinical trials and everyday practice.

Disclosures

Dr Hammami has no relevant conflicts of interest to disclose.

Suggested Reading

Friedman S, Magnussen B, O'Toole A, et al. Increased use of medications for erectile dysfunction in men with ulcerative colitis and Crohn's disease compared to men without inflammatory bowel disease: a nationwide cohort study. *Am J Gastroenterol*. 2018;113(9):1355-1362.

Hammami MB, Mahadevan U. Men with inflammatory bowel disease: sexual function, fertility, medication safety, and prostate cancer. *Am J Gastroenterol*. 2020;115(4):526-534.

Lindsey I, George B, Kettlewell M, Mortensen N. Randomized, double-blind, placebo-controlled trial of sildenafil (Viagra) for erectile dysfunction after rectal excision for cancer and inflammatory bowel disease. *Dis Colon Rectum*. 2002;45(6):727-732.

Mouyis M, Flint JD, Giles IP. Safety of anti-rheumatic drugs in men trying to conceive: a systematic review and analysis of published evidence. *Semin Arthritis Rheum*. 2019;48(5):911-920.

O'Toole A, de Silva PS, Marc LG, et al. Sexual dysfunction in men with inflammatory bowel disease: a new IBD-specific scale. *Inflamm Bowel Dis*. 2018;24(2):310-316.

Shmidt E, Suárez-Fariñas M, Mallette M, et al. Erectile dysfunction is highly prevalent in men with newly diagnosed inflammatory bowel disease. *Inflamm Bowel Dis*. 2019;25(8):1408-1416.

Tavernier N, Fumery M, Peyrin-Biroulet L, et al. Systematic review: fertility in non-surgically treated inflammatory bowel disease. *Aliment Pharmacol Ther*. 2013;38(8):847-853.

Zhao S, Wang J, Liu Y, et al. Inflammatory bowel diseases were associated with risk of sexual dysfunction in both sexes: a meta-analysis. *Inflamm Bowel Dis*. 2019;25(4):699-707.