Clinical Gastroenterology and Hepatology 2018;■:■–■

Paternal Disease Activity Is Associated With Difficulty in Conception Among Men With Inflammatory Bowel Diseases

Ashwin N. Ananthakrishnan,[*] Christopher Martin,[‡] Sunanda Kane,[§] Robert S. Sandler,[‡] and Millie D. Long[‡]

*Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; [‡]Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina, Chapel Hill, North Carolina; and [§]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota

The impact of inflammatory bowel disease (IBD) activity and treatment on fertility and pregnancy outcomes is important for men and women. In women, remission at conception determines better pregnancy outcomes,[1,2] and most maternal IBD medication exposures are safe.[2] In contrast, less is known about the impact of paternal disease activity and medication use on fertility and pregnancy outcomes in men with IBD.[3]

Methods

We surveyed a large Internet-based voluntary cohort of patients with Crohn's disease or ulcerative colitis (the IBD Partners cohort), who complete comprehensive surveys at baseline and update changes in disease and treatment biannually.[4] For this study, all male participants were offered an optional survey comprising detailed questions on the first successful pregnancy with their partners including number of months to conception, need for assisted reproductive techniques, self-reported disease activity in the 6 months preceding conception, and medical and surgical treatment history at the time of conception. For participants who had not successfully conceived, information regarding whether infertility care was sought and contributing maternal and paternal factors were ascertained. Our primary outcome was difficulty conceiving, defined as >6 months to conceive or seeking fertility treatment in the absence of maternal factors. Our secondary outcomes were presence of congenital anomalies, low birth weight, or preterm birth. Regression models adjusting for potential confounders including paternal and maternal age and maternal complications during pregnancy assessed the effect of disease activity and treatment on study outcomes.

Results

Of the 455 respondents to the initial survey, the final analysis included 256 men who had either successfully conceived or attempted to conceive a child with their partner (mean age at attempt, 30 years; 66% with Crohn's disease). Difficulty conceiving was reported by 77 men (30%). Those with difficulty conceiving were older (32 vs 29 years) than those without difficulty. Men who were diagnosed with IBD before this pregnancy were more likely to report difficulty conceiving than those who were diagnosed after the pregnancy (38% vs 20%; $P = .002$; multivariable odds ratio [OR] adjusting for maternal and paternal age, 1.99; 95% confidence interval [CI], 1.05–3.78). Among 154 patients with IBD diagnosed prior, one-quarter each were on steroids (24%), thiopurines (25%), and biologics (22%), and half were on aminosalicylates (52%). Compared with those without a diagnosis of IBD before pregnancy (20%), participants with active or recently active disease were more likely to have had difficulty conceiving (45%; OR, 2.62; 95% CI, 1.34–5.13); this effect was not noted for those with a prior diagnosis but in sustained remission (21%; OR, 0.93; 95% CI, 0.37–2.33) (Figure 1). Male participants with active IBD (16%) or inactive IBD (14%) before pregnancy were more likely to need assisted reproductive techniques than participants without IBD prior (4%; $P = .017$). Aminosalicylate use was associated with difficulty conceiving on univariate (47% vs 25%; $P = .009$) but not multivariable analysis when adjusting for recent disease activity (OR, 1.98; $P = .09$). Smoking status, duration of disease, or surgical treatments for Crohn's disease or ulcerative colitis were not associated with difficulty conceiving. There was no increase in risk of birth defects with paternal exposure to biologics (OR, 0.50; 95% CI, 0.05–5.20), thiopurine (OR, 0.49; 95% CI, 0.05–4.82), or corticosteroid therapy (OR, 1.80; 95% CI, 0.30–10.94).

Discussion

The primary finding of our study was that men with IBD who reported difficulty or delay in conceiving were more likely to have had active or recently active disease

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2018.04.001

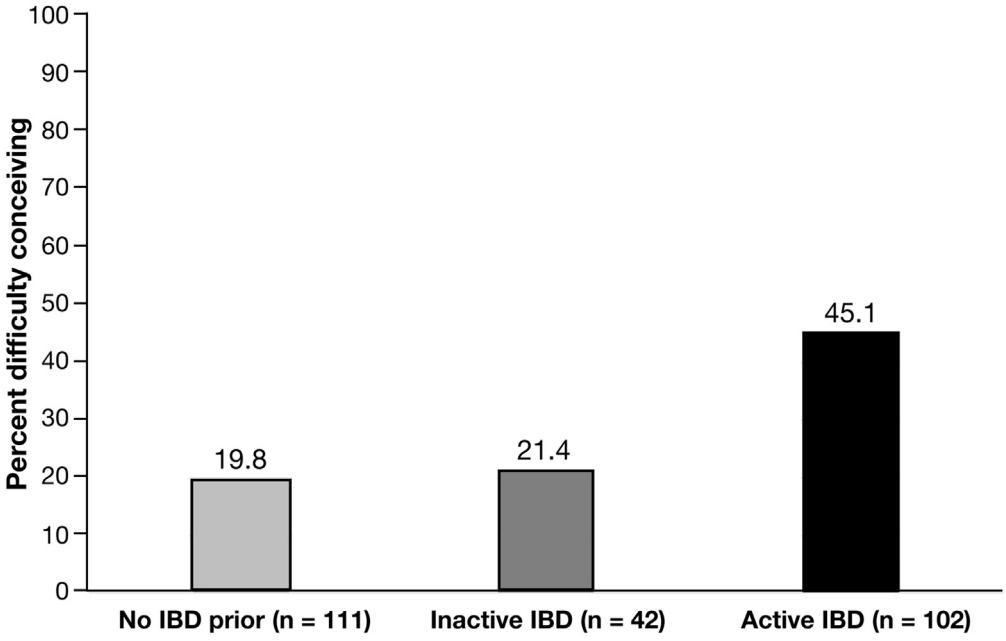

Figure 1. Rates of difficulty conceiving, by inflammatory bowel disease status. Difficulty conceiving defined as requiring >6 months of attempts for conception, requiring assisted reproductive techniques, or visiting a specialist for fertility evaluation.

than men who reported no delay. We hypothesize that this association may be mediated by several factors that may affect desire for sexual activity, semen characteristics, or both. These include impact of symptoms; effect of systemic or pelvic inflammation; adverse effects of medications; or impact of comorbidity, such as anxiety and depression. Although some studies have reported no impact of IBD on semen characteristics, fertility rates, and pregnancy outcomes, few studies have examined the effect of disease activity. There is a need to examine whether elevated circulating or fecal inflammatory markers impacts semen characteristics, and through that, reduces fertility. Consistent with some prior reports,[5,6] aminosalicylate users were more likely to report a delay in conception compared with nonusers, although at least part of this association may be mediated by inadequate disease control. Reassuringly, none of the medications when used by the father were associated with low birth weight, preterm birth, or congenital anomalies consistent with recent cohort studies.[7,8] In conclusion, our findings suggest that when attempting to begin a family, ensuring optimal control of disease may also be important in men with IBD.

References

1. de Lima A, Zelinkova Z, Mulders AG, et al. Preconception care reduces relapse of inflammatory bowel disease during pregnancy. Clin Gastroenterol Hepatol 2016;14:1285–1292.
2. McConnell RA, Mahadevan U. Pregnancy and the patient with inflammatory bowel disease: fertility, treatment, delivery, and complications. Gastroenterol Clin North Am 2016;45:285–301.
3. Narendranathan M, Sandler RS, Suchindran CM, et al. Male infertility in inflammatory bowel disease. J Clin Gastroenterol 1989;11:403–406.
4. Long MD, Kappelman MD, Martin CF, et al. Development of an Internet-based cohort of patients with inflammatory bowel diseases (CCFA Partners): methodology and initial results. Inflamm Bowel Dis 2012;18:2099–2106.
5. Kjaergaard N, Christensen LA, Lauritsen JG, et al. Effects of mesalazine substitution on salicylazosulfapyridine-induced seminal abnormalities in men with ulcerative colitis. Scand J Gastroenterol 1989;24:891–896.
6. Riley SA, Lecarpentier J, Mani V, et al. Sulphasalazine induced seminal abnormalities in ulcerative colitis: results of mesalazine substitution. Gut 1987;28:1008–1012.
7. Larsen MD, Friedman S, Magnussen B, et al. Birth outcomes in children fathered by men treated with anti-TNF-alpha agents before conception. Am J Gastroenterol 2016;111:1608–1613.
8. Norgard BM, Magnussen B, Larsen MD, et al. Reassuring results on birth outcomes in children fathered by men treated with azathioprine/6-mercaptopurine within 3 months before conception: a nationwide cohort study. Gut 2017;66:1761–1766.

Reprint requests
Address requests for reprints to: Ashwin N. Ananthakrishnan, MD, MPH, Crohn's and Colitis Center, Massachusetts General Hospital, Harvard Medical School, 165 Cambridge Street, 9th Floor, Boston, Massachusetts 02114. e-mail: tpetrovic@gastro.org; fax: 617-726-3080.

Acknowledgments
The authors acknowledge the valuable contributions of the participants and the research staff of the Crohn's and Colitis Foundation IBD Partners cohort.

Conflicts of interest
These authors disclose the following: Ashwin N. Ananthakrishnan serves on scientific advisory boards for Abbvie, Takeda, and Gilead; and is a consultant for Seres therapeutics. Sunanda Kane is a consultant for Abbvie, Janssen, Samsung Bioepis, 11 Health, Spherix Global Health, Seres therapeutics; has received research funding UCB; and is on the GI Specialty Board at ABIM. The remaining authors disclose no conflicts.

Funding
This research was supported, in part, by a grant from the National Institutes of Health (P30 DK034987).