



Published in final edited form as:

*Clin Gastroenterol Hepatol.* 2019 January ; 17(1): 203–204. doi:10.1016/j.cgh.2018.04.001.

## Paternal disease activity is associated with difficulty in conception among men with inflammatory bowel diseases

Ashwin N Ananthakrishnan<sup>1</sup>, Christopher Martin<sup>2</sup>, Sunanda Kane<sup>3</sup>, Robert S. Sandler<sup>2</sup>, and Millie D. Long<sup>2</sup>

<sup>1</sup>Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, MA

<sup>2</sup>Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina, Chapel Hill, NC

<sup>3</sup>Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN

### Keywords

paternal; Crohn's; fertility; active disease

## INTRODUCTION

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

Correspondence: Ashwin N Ananthakrishnan, MD, MPH, Crohn's and Colitis Center, Massachusetts General Hospital, Harvard Medical School, 165 Cambridge Street, 9<sup>th</sup> Floor, Boston, MA 02114, aananthakrishnan@mg.harvard.edu, Phone: 617-724-9953, Fax: 617-726-3080.

### Author contributions:

Ananthakrishnan: designing survey, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content.

Martin: Statistical analysis, interpretation of data, critical revision of the manuscript for important intellectual content.

Kane: designing survey, interpretation of data, critical revision of the manuscript for important intellectual content.

Sandler, Long: interpretation of data, critical revision of the manuscript for important intellectual content, supervision of the study cohort.

### Conflicts of Interest:

Ananthakrishnan: Scientific advisory boards for Abbvie, Takeda, and Gilead. Consultant for Seres therapeutics

Martin: None

Kane: Consultant for Abbvie, Janssen, Samsung Bioepis, 11 Health, Spherix Global Health, Seres therapeutics; Research funding UCB; Other: GI Specialty Board ABIM

Sandler: None

Long:

**Publisher's Disclaimer:** This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

## METHODS

We surveyed a large internet-based voluntary cohort of patients with Crohn's disease (CD) or ulcerative colitis (UC) (the IBD Partners cohort), who complete comprehensive surveys at baseline and update changes in disease and treatment bi-annually<sup>4</sup>. 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 (ART), self-reported disease activity in the 6 months preceding conception, as well as 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 (LBW) or pre-term 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 CD). 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 prior to this pregnancy were more likely to report difficulty conceiving than those were diagnosed after the pregnancy (38% vs. 20%,  $p=0.002$ ; 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%), biologics (22%) and half were on aminosalicylates (52%). Compared to those without a diagnosis of IBD prior to 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%) prior to pregnancy were more likely to need ART than participants without IBD prior (4%,  $p=0.017$ ). Aminosalicylate use was associated with difficulty conceiving on univariate (47% vs. 25%,  $p=0.009$ ) but not multivariable analysis when adjusting for recent disease activity (OR 1.98,  $p=0.09$ ). Smoking status, duration of disease, or surgical treatments for CD or UC 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 than men who

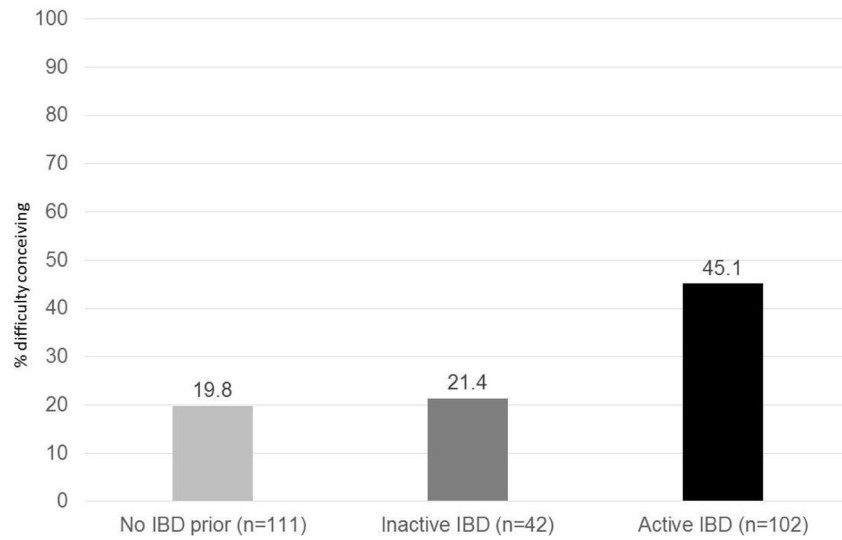
reported no delay. We hypothesize that this association may be mediated by several factors that may affect desire for sexual activity, semen characteristics, or both. These include impact of symptoms, effect of systemic or pelvic inflammation, adverse effects of medications, or impact of comorbidity such as anxiety and depression. While 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<sup>5, 6</sup>, aminosalicylate users were more likely to report a delay in conception compared to non-users though 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 LBW, preterm birth or congenital anomalies consistent with recent cohort studies<sup>7, 8</sup>. 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.

## Acknowledgments

We acknowledge the valuable contributions of the participants and the research staff of the Crohn's and Colitis Foundation IBD Partners cohort. The research was supported, in part, by a grant from the NIH (P30 DK034987)

## 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; 14:1285–1292e1. [PubMed: 27001269]
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. [PubMed: 27261899]
3. Narendranathan M, Sandler RS, Suchindran CM, et al. Male infertility in inflammatory bowel disease. *J Clin Gastroenterol*. 1989; 11:403–6. [PubMed: 2760429]
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; 18:2099–106. [PubMed: 22287300]
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; 24:891–6. [PubMed: 2572047]
6. Riley SA, Lecarpentier J, Mani V, et al. Sulphasalazine induced seminal abnormalities in ulcerative colitis: results of mesalazine substitution. *Gut*. 1987; 28:1008–12. [PubMed: 2889648]
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. [PubMed: 27619836]
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. [PubMed: 27456154]



**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