Maternal inflammatory bowel disease, racial diversity and adverse birth outcomes

Zubair Saeed, MD,¹ Hany Aly, MD,² Charles Macri, MD,³ Dinan Abdelatif, BA,³ Mohamed A. Mohamed, MD,^{3,4}

Keywords: Birth outcomes, Crohn's disease, inflammatory bowel disease, prematurity, ulcerative colitis

Abstract

Background: Inflammatory bowel disease (IBD) is a term used to describe two conditions, Crohn's disease and ulcerative colitis (UC), that currently have no definite cure. The incidence of IBD worldwide has increased, frequently affecting women during their reproductive years.

Objectives: This study examines the association of Crohn's disease and ulcerative colitis (UC) with adverse pregnancy outcomes and looks at the interactions of race/ethnicity on these associations.

Study Design: We examined hospital birth records in the National Inpatient Sample (NIS) data sets in 2011 and 2012. We identified maternal demographics and clinical characteristics using international classification of disease-9 codes. Chi-square and Fisher exact tests were used to examine associations and logistic regression models were used to control for confounders.

Results: Crohn's disease is associated with small for gestational age, aOR 1.70(Cl:1.53-

1.89,p<0.001) but not premature delivery, whereas UC was associated with prematurity, aOR 1.5(Cl:1.36-1.66,p<0.001) to a greater extent than with SGA. Analyses by race/ethnicity showed Crohn's disease to be associated with SGA among newborns of all racial groups, but most evident among African Americans, aOR 2.55(Cl:2.06-3.15,p<.001). Crohn's disease was associated with prematurity only in Caucasian women, aOR 1.21(Cl:1.10-1.34,p<.001). UC was associated with SGA newborns only in Hispanic mothers, aOR 3.40(Cl:2.24-5.15,p<0.001), and with premature delivery only among Caucasian mothers, aOR 1.60(Cl:1.42-1.80,p<.001).

Conclusion: Both Crohn's disease and ulcerative colitis are associated with prematurity and small for gestational age in a way that is significantly affected by maternal race. Qualitative studies are needed to understand mechanisms for these associations and the role of race/ethnicity.

¹Fairfax County Health Department, Fairfax, Virginia

²Department of Neonatology, Cleveland Clinic Children's Hospital, Cleveland, Ohio

³Department of Obstetrics and Gynecology, the

Please cite this paper as: Saeed Z, Aly H, Macri C, Abdelatif D, Mohamed MA. Maternal inflammatory bowel disease, racial diversity and adverse birth outcomes. Proc Obstet Gynecol. 2020;10(1):Article 3 [16 p.]. Available from: http://ir.uiowa.edu/ Free full text article.

Corresponding author: Mohamed A. Mohamed, MD, The George Washington University Hospital, Newborn Services, Washington, DC 20037, <u>mmohamed@gwu.edu</u>

Financial Disclosure: The authors report no conflict of interest.

Copyright: © 2020 Saeed et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

George Washington University Hospital, Washington, DC ⁴Newborn Services Division, the George Washington University Hospital, Washington, DC.

Introduction

Crohn's disease and ulcerative colitis (UC) are two chronic relapsing and remitting diseases that currently have no definitive cure and together compromise conditions known а class of as inflammatory bowel disease (IBD).^{1,2} In the United States, the incidence of Crohn's disease has been 3.1 to 14.6 cases per 100,000 person years and the prevalence is 201 per 100.000 adults, whereas the incidence of UC is 2.2 to 14.3 cases per 100,000 person years and the prevalence is 238 per 100,000 adults.^{1,2} IBD has long been considered a problem of Western societies due to certain lifestyle factors thought to contribute to its pathogenesis.³ However, data from recent years indicates that the incidence of IBD is on the rise worldwide, including in Eastern and developing countries.^{4,5} In addition, younger industrialized urban populations in societies are more frequently affected with IBD and, as a result, women during their reproductive years are affected.⁶

Previous studies have linked maternal IBD with low birthweight, small for gestational age (SGA), and preterm deliverv outcomes in neonates. However, these studies were either conducted outside of the United States7-¹² or were limited to a small sample size.¹³⁻¹⁶ In fact, a systematic review of past studies revealed inconsistencies in study size, quality and design, making it difficult to precisely assess the relationship between IBD and adverse birth outcomes.¹⁷⁻¹⁹ In addition, the relationship between IBD and race/ethnic

groups with regard to adverse birth outcomes has not been previously addressed. Therefore, a study is needed to present data from across the United States taking into consideration race/ethnicity, in addition to other variables such as age, behavioral, socioeconomic and clinical characteristics.

In this study we utilized the National Inpatient Sample (NIS) datasets, which include data from most states and regions of the United States. We examined the association between IBD in pregnant women and the risk for adverse birth outcomes. The specific aims of this study were to: 1) examine the association of Crohn's disease in pregnant women with preterm delivery or SGA newborns while controlling for maternal demographic and clinical variables, 2) examine the association of UC with preterm delivery or SGA, and 3) examine the implication of maternal race/ethnicity on these associations.

Methods

<u>Data Source</u>

We used de-identified datasets obtained from the Healthcare Cost and Utilization Project (HCUP) associated with the Federal Agency for Healthcare Research and Quality (AHRQ).²⁰ The HCUP database is one of the largest healthcare databases in the United States that produces several datasets including the National Inpatient Sample (NIS). The NIS dataset is reproduced annually from an all-payer national database that has collected millions of inpatient hospitalization records from 1993 up to 2012. These datasets have hospitalization records from more than 1,000 hospitals across 45 states with

various care levels (primary-tertiary), types of insurance (public, private) and academic settings (university-general). Clinical data on hospitalization records are coded for each patient using International Classification of Disease -9th version (ICD-9). Current Procedural Terminology (CPT) are used to code surgical and non-surgical procedures done during patients' hospitalizations. The NIS dataset includes more than 100 data elements for each hospital stay, such primary and secondarv as and secondary diagnoses, primary of admission, procedures, source disposition at discharge, patient demographics. expected payment source and total charges.

Sample identification

We included hospital records for pregnant women who gave birth to viable newborns in the years 2011 and 2012. We selected only these two years from the NIS data available from 1993-2012 to avoid multiple inclusions of same women with repeated pregnancies. Pregnant women who transferred out of the hospital of birth were excluded to avoid duplicate inclusion at both birthing and receiving hospitals. We used ICD-9 diagnostic codes: 555, 5550, 5551, 5552, and 5559 to identify preexisting or recently diagnosed Crohn's disease, and 556, 5560, 5561, 5562, 5563, 5564, 5565, 5566, 5568, and 5569 to identify preexisting or recently diagnosed UC in women admitted for birthing. Preterm delivery was identified when a live delivered offspring was before completing 37 weeks of gestation.²¹ We used ICD-9 diagnostic codes 6442, 64420, and 64421 to identify preterm deliveries. Small for destational age (SGA) was defined as birthweight below the 10th percentile.22 We used ICD-9

diagnostic codes: 6565, 65650, 65651, 65653 to identify small for and gestational age newborns. We included potential demographic and clinical characteristics that may correlate with preterm delivery or SGA outcomes in our analysis as potential confounding factors using respective ICD-9 codes. Confounders included maternal age, hypertension, cardiovascular race. diseases, diabetes mellitus. renal diseases, anemia, thyroid diseases, chorioamnionitis, coagulation disorder, smoking or drug seizures, obesity, placenta previa. abuse. placental abruption, twin gestation and type of insurance coverage.

Statistical analysis

We used a retrospective cross-sectional study design to run this analysis. We identified two main groups in the sample, pregnant women with or without IBD. We created two subgroups for those with or without Crohn's disease and those with or without UC. We used SAS 9.1 (SAS Institute, Cary, NC, USA) to run our statistical analysis. We used frequency analyses to calculate prevalence of inflammatory bowel diseases, Crohn's disease, UC, adverse birth outcomes (preterm delivery and SGA newborns), and other demographic and clinical characteristics in each group and subgroup. We calculated unadjusted odds ratios (ORs), 95% Confidence Intervals (CI) and p-value for all demographic and clinical variables for both IBD groups using Chi-square and Fisher exact tests. Logistic regression models were used to calculate adjusted ORs for the association of IBD (and subsequently for both Crohn's disease or UC) with preterm delivery and SGA while controlling for status the demographic and clinical characteristics

mentioned above. Furthermore, adjusted ORs examining the association of Crohn's disease and UC with preterm delivery and SGA were calculated within each race/ethnicity. We considered *p*value to be statistically significant if it was < 0.05. This study was conducted with Internal Review Board (IRB) approval from the George Washington University Hospital.

Results

The weighted data set included 8,273,987 pregnant women with the following racial/ethnic distribution: 47.9% White, 14.0% African American, 20.3% Hispanic. Pregnant women ages 13-17 years old represented 2.5% of the sample while women >35 years old represented 14.8%. ICD-9 diagnostic codes for IBD were identified in 14,476 (0.18%) hospital discharge records; (Crohn's disease in 0.11% and UC in 0.07% of the population). Preterm delivery occurred in 6.08% of the cases and 2.34% delivered SGA newborns.

Data for the study include the following generalizations. Pregnant women with IBD were mostly white (69.4%). IBD was less common in teenage mothers (0.6% vs 2.5%, p<0.001) but more frequent in pregnant women \geq 35 years old (18.1% vs. 14.8%, p<0.001). Pregnant women with IBD were more frequently identified with cardiovascular, renal, thyroid,

anemia, seizure and coagulation disorders as well as with a higher prevalence of placental abruption, and increased alcohol or drug abuse. However, pregnant women with IBD were less likely to be obese, have chorioamnionitis or be covered by public insurance. Table (1) shows frequencies, percentages and adjusted odds ratios (aOR) for the demographic and clinical characteristics of the study population. Figure 1 demonstrates the association of preterm delivery and SGA newborns with IBD and its subtypes (Crohn's disease and UC) in the overall population after adjusting for confounding variables.

IBD is associated with preterm delivery, aOR 1.24 (CI: 1.17-1.33, p<0.001), and small for gestational age, aOR 1.57 (CI:1.44-1.71, p<0.001). Further analysis of each of the IBD subtypes, Crohn's disease and UC, revealed significant differences in the association of each disease with the examined birth outcomes. Crohn's disease was not generally associated with preterm deliveries. but was significantly associated with SGA, aOR 1.70 (CI: 1.53-1.89, *p*<0.001). In contrast, UC was more likely to be associated with preterm deliveries, aOR 1.50 (CI: 1.36-1.66, p<0.001) than with SGA, aOR 1.31 (CI: 1.08-1.59, p=0.001) after adjusting for demographic and clinical confounders in the logistic regression models (Figure 1).

	Women with IBD, n (%) n=14,476	Women without IBD, n (%) n=8,355,987	Adjusted OR (CI), p-value
Maternal age groups 18 – 34 Years <18 Years <u>></u> 35 Years	11,762 (81.3) 92 (0.6) 2622 (18.1)	6,826,561 (82.7) 208,253 (2.5) 1,221,173 (14.8)	1 (reference) 0.34 (0.27 – 0.41), p<.0001 1.14 (1.09 – 1.19), p<.0001
Race White African American Hispanic Asian Natives	10,052 (69.4) 1610 (11.1) 835 (5.8) 142 (0.98) 44 (0.3)	3,956,441 (47.9) 1,159,501 (14.0) 1,681,385 (20.4) 382,300 (4.6) 64,778 (0.8)	1 (reference) 0.60 (0.57 – 0.64), p<.0001 0.24 (0.22 – 0.25), p<.0001 0.14 (0.12 – 0.17), p<.0001 0.30 (0.22 – 0.40), p<.0001
Twin gestation	315 (2.2)	115,387 (1.4)	1.25 (1.12 – 1.40), p<.0001
Hypertension	1559 (10.8)	851,730 (10.3)	0.96 (0.91 - 1.02), p=0.161
Chorioamnionitis	108 (0.8)	75,869 (0.9)	0.79 (0.65 - 0.95), p=0.014
Diabetes mellitus	169 (1.2)	107,116 (1.3)	0.93 (0.80 - 1.08), p=0.330
Cardiovascular diseases	243 (1.7)	56,783 (0.7)	1.95 (1.71 - 2.21), p<0.001
Renal diseases	719 (5.0)	209,776 (2.5)	2.06 (1.91 - 2.22), p<0.001
Maternal anemia	2801 (19.4)	988,773 (12.0)	1.94 (1.86 - 2.02), p<0.001
Thyroid diseases	702 (4.9)	238,269 (2.9)	1.35 (1.25 - 1.46), p<0.001
Seizure disorders	138 (0.95)	34,461 (0.42)	2.07 (1.75 – 2.45), p<0.001
Coagulation disorders	323 (2.23)	119,837 (1.45)	1.25 (1.12 – 1.40), p<0.001
Placenta previa	100 (0.7)	55,531 (0.7)	0.86 (0.71 - 1.05), p=.158
Placental abruption	197 (1.4)	86,192 (1.0)	1.22 (1.06 - 1.40), p=.007
Obesity	577 (4.0)	403,819 (4.9)	0.79 (0.73 – 0.86), p<0.001
Smoking	912 (6.3)	441,590 (5.4)	1.04 (0.97 – 1.11), p<0.339
Alcohol use	20 (0.14)	3154 (0.04)	3.28 (2.11 – 5.10), p<0.001
Drug use	166 (1.15)	39,755 (0.48)	1.94 (1.66 – 2.27), p<0.001
Public insurance	4036 (27.9)	3,738,911 (45.3)	0.55 (0.53 – 0.57), p<0.001
Preterm Delivery	1099 (7.59)	501,717 (6.07)	1.24 (1.17 - 1.33), <i>p</i> <0.001
Small for Gestational Age	541 (3.74)	193,344 (2.34)	1.57 (1.44 - 1.71), <i>p</i> <0.001

Table 1: Demographic and clinical characteristics of pregnant women with and without inflammatory bowel disease (IBD)*

*Confounding variables controlled for in the logistic regression model for the weighted sample included maternal age, race, hypertension, cardiovascular and renal diseases, diabetes mellitus, anemia, thyroid disorders, chorioamnionitis, coagulation disorder, seizures, obesity, smoking or drug abuse, placenta previa, placental abruption, twin gestation and type of insurance coverage

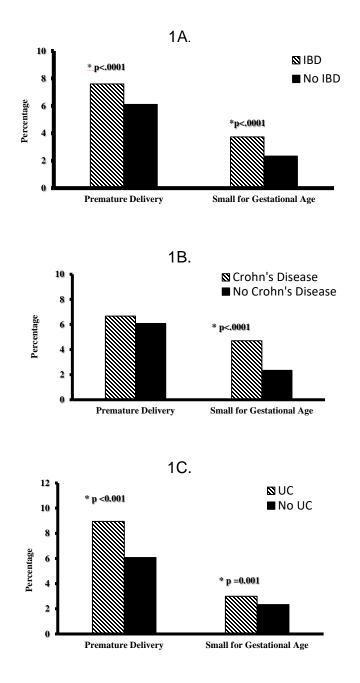


Figure 1: Preterm delivery and small for gestational age (SGA) in pregnant women with and without inflammatory bowel disease (IBD) in Figure 1A, Crohn's disease in Figure 1B and ulcerative colitis (UC) in Figure 1C.

Maternal IBD and adverse birth outcomes

The analysis was repeated separately controlling for race/ethnicity. In general, the impact of Crohn's disease on pregnancy outcomes was different from that of UC within each race/ethnicity. Although, Crohn's disease was not associated with preterm delivery in the overall sample, it was significantly associated with preterm delivery among White women, aOR 1.21 (CI: 1.10-1.34, p<.001). Crohn's disease was associated with increased SGA among newborns of all three racial groups, with the greatest association observed among African Americans, aOR 2.55 (CI: 2.06-3.15, p<.001), (Figure 2).

	Women with Crohn's (%)	Women without Crohn's (%)	Adjusted OR (CI)	p-value				
Preterm delivery among women with Crohn's disease compared to those without								
Overall sample	6.76	6.08	1.09 (1.00-1.19)	p = 0.05				
White	7.01	5.6	1.21 (1.10-1.34)	<i>p</i> <0.001				
African American	7.18	8.08	0.87 (0.70-1.10)	<i>p</i> = 0.23				
Hispanic	4.87	6.02	0.66 (0.41-1.06)	p = 0.09				
Small for gestational age among women with Crohn's disease compared to those without								
		2.24		0.001				
Overall sample	4.17	2.34	1.70 (1.53-1.89),	<i>p</i> <0.001				
White	3.26	2.34	1.38 (1.20-1.59),	<i>p</i> <0.001				
African American	7.92	3.27	2.55 (2.06-3.15),	<i>p</i> <0.001				
Hispanic	3.69	1.58	(1.14-3.34),	P = 0.015				

Table 2: Adverse birth outcomes associated with Crohn's disease*

*Confounding variables controlled for in the logistic regression model for the weighted sample included maternal age, hypertension, cardiovascular and renal diseases, diabetes mellitus, anemia, thyroid disorders, chorioamnionitis, coagulation disorder, seizures, obesity, smoking or drug abuse, placenta previa, placental abruption, twin gestation, and type of insurance coverage

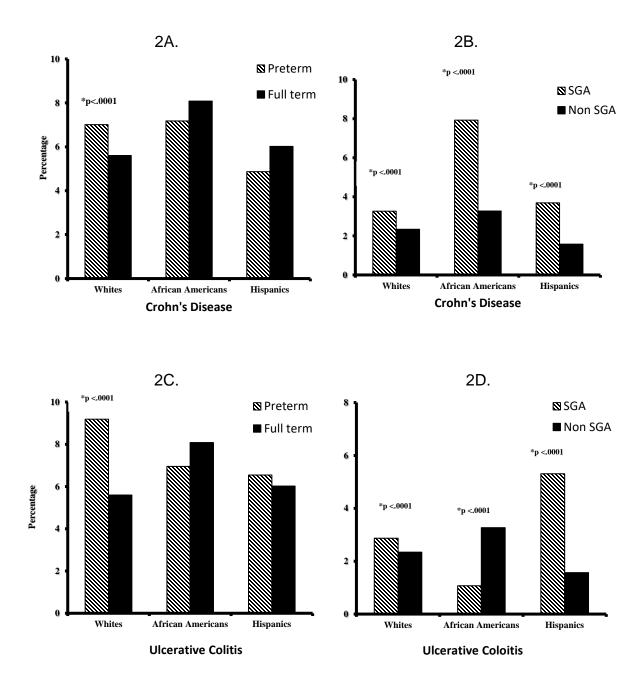


Figure 2: Preterm delivery and small for gestational age (SGA) among pregnant women with and without Crohn's disease and ulcerative colitis (UC) in different race/ethnic groups. Figures 2A and 2B compare preterm delivery and SGA between Whites, African Americans, and Hispanics with Crohn's disease, respectively. Figures 2C and 2D compare preterm delivery and SGA between Whites, African Americans, and Hispanics with UC, respectively. Although UC was associated with preterm delivery in the overall sample, it was in fact, found to be closely associated with preterm delivery only among White women, aOR 1.60 (CI: 1.42-1.80, p<.001). No significant association of UC with preterm delivery was noted among African American or Hispanic women. SGA newborns, on the other hand, were more common in

women with UC among both Hispanic and White pregnant women, with a much greater association observed among Hispanics, aOR 3.40 (CI: 2.24-5.15, p<0.001) than among Whites. In contrast, African American women with UC delivered fewer SGA newborns than women with no UC, aOR 0.33 (CI: 0.13-0.83, p=0.019), (Figure 2).

	Women with UC (%)	Women without UC (%)	Adjusted OR (CI),	p-value					
Preterm delivery among women with ulcerative colitis									
Overall sample	8.95	6.08	1.50 (1.36-1.66)	p <0.001					
White	9.19	5.6	1.60 (1.42-1.80)	p <0.001					
African American	6.95	8.08	0.90 (0.62-1.32)	p = 0.60					
Hispanic	6.54	6.02	1.09 (0.74-1.60)	p = 0.66					
Small for gestational age among women with ulcerative colitis compared to those without									
Overall sample	3	2.34	1.31 (1.08-1.59)	p = 0.001					
White	2.87	2.34	1.28 (1.04-1.54)	p = 0.007					
African American	1.07	3.27	0.33 (0.13-0.83)	p = 0.019					
Hispanic	5.31	1.57	(2.24-5.15)	p <0.001					

Table 3: Adverse birth outcomes associated with ulcerative colitis (UC)*

*Confounding variables controlled for in the logistic regression model for the weighted sample included maternal age, hypertension, cardiovascular and renal diseases, diabetes mellitus, anemia, thyroid disorders, chorioamnionitis, coagulation disorder, seizures, obesity, smoking or drug abuse, placenta previa, placental abruption, twin gestation, and type of insurance coverage

Discussion

Principal Findings

This study demonstrated significant increase in preterm delivery and SGA newborns among pregnant women with IBD after adjusting for clinical confounders known to increase the likelihood of both adverse birth outcomes. The associations of preterm delivery with both Crohn's disease and UC were only evident among the White population. However, SGA was associated with both diseases in all races except African Americans with UC.

<u>Results</u>

IBD was associated with both premature delivery and SGA. Previous studies have reached different conclusions; some

Maternal IBD and adverse birth outcomes

studies indicated an association between prematurity and SGA birth with IBD, while other studies have found no such association in one or both of the IBD subtypes.²³⁻²⁸ A meta-analysis bv Cornish et al., which included data from 12 studies on 3.907 patients with IBD and 320,531 subjects without IBD, found that women with IBD had increased risk of preterm delivery, but not of SGA birth.¹⁴ A meta-analysis by O'Toole et al., which included data from 23 studies on 15,007 patients with IBD and 4.614.271 subjects without IBD, found that women with IBD had a significantly increased risk for both preterm delivery and SGA. Although findings of this meta-analysis were like ours, we observed a stronger association with SGA birth than with preterm delivery. Moreover, we stratified outcomes according to IBD subtypes and controlled for several potential confounding factors.

To the best of our knowledge, this study is the first to assess birth outcome risks in IBD population stratified by race/ethnic groups. In Whites, both Crohn's disease and UC were associated with premature birth and SGA newborn outcomes. showing the most significant association for UC with preterm deliveries. In African Americans, neither Crohn's disease nor UC was associated with preterm delivery. Meanwhile, the association of both IBD subtypes differed in relation to SGA newborn outcomes. Crohn's disease was associated more with SGA, while UC was associated less with SGA. These paradoxical findinas need further qualitative studies to understand the underlying nutritional cultural. or psychological factors. In Hispanics, association with premature birth was not increased with either Crohn's disease or UC, but association with SGA newborns increased with both diseases, with a stronger association between UC and SGA. Unlike preterm delivery, SGA was associated with both Crohn's disease and UC in each of the race/ethnic subgroups: Whites, African Americans and Hispanics. However, the nature and magnitude of these associations differed according to both the disease (Crohn's disease vs. UC) and race. In Crohn's disease, the greatest association with SGA was seen in African Americans followed by Hispanics, then Whites. In UC, SGA was mostly associated with Hispanics followed by Whites.

Clinical Implications

Although the exact etiology of IBD remains unclear. several factors including genetics and environment are thought to be involved. Microorganisms such as bacteria and viruses, and sensitivity to protein in foods have been linked to these conditions.²⁹⁻³² In addition to its inflammatory effect at the maternal fetal interface, Crohn's disease or resection of small bowel as treatment for Crohn's disease may interfere with gastrointestinal absorption of nutrients that could compromise transfer of microand macro-nutrients from mother to fetus leading to increased risk of SGA birth.³² Furthermore, patients who are very ill with active Crohn's disease and UC and who do not respond to medical therapy may have reduced food consumption. In addition. IBD is associated with innate immune deficits including those of tolllike receptor (TLR) signaling and NODlike receptor signaling in addition to deficiency of defensins and autophagy pathways.³³ These defects are likely involved in the abnormal mucosal in IBD, but response seen TLR irregularities are also hypothesized to cause delivery-inducing release of procytokines inflammatory and

prostaglandins in response to microbial stimuli. Another theory is that the role of increased gut permeability during increased inflammation could alter nutritional and immunological factors affecting delivery.³⁰

The increased perinatal morbidity in patients with Crohn's disease and UC could be due in part to a variety of extraintestinal manifestations of IBD, especially inflammatory conditions of the liver and joints, and arterio-venous pathologies. thromboembolic These inflammatory disorders have genetic correlates, notably that human leukocyte antigens and their pathogenesis include T-cell activity and that imbalances in cvtokine production and intestinal antigens are shared by other organs.²⁸⁻³³ The association of preterm delivery with Crohn's disease and UC is plausibly related to such mechanisms that are common in both subtypes of IBD. More qualitative and delivery-related studies are needed to understand the underlying mechanisms (genetic, environmental, or biological) of adverse neonatal outcomes in women with IBD.

This study can increase the awareness of health care providers with regard to the differential impact of each subtype of IBD; Crohn's disease and UC, on birth outcomes, and can, therefore, enable them to offer more specific counseling and comprehensive clinical care to pregnant women according to their specific illness. Such tailored counseling would be provided according to maternal race/ethnic background. For example, pregnant women with Crohn's disease could be counseled for their increased risk of small for gestational age outcomes, especially those of African American or Hispanic descent. White women with ulcerative colitis could be

counseled for their increased risk of prematurity, while those of Hispanic origin could be counseled for their increased risk for small for gestational age. In this way, health care providers would be able to enhance their monitoring for early signs of fetal growth restriction or preterm labor according to each peculiarities of each disease and within each race/ethnicity respectively.

Research Implications

Future research on the association of maternal IBD with adverse neonatal outcomes should focus on analyzing the impact of additional predictors for prematurity and SGA. Our study stratified odd ratios according to maternal race, but additional stratification according to maternal age, neonatal sex or clinical conditions could also be performed. In addition, risk factors common to both preterm and SGA birth, such as low weight gain during pregnancy, maternal short stature and maternal stress level, ³⁸ could be analyzed in future studies for their impact on women with IBD.

Strengths and limitations

This study benefited from several strengths. Foremost, the study was conducted using a national in-hospital dataset while previous studies were limited to small samples or to statelimited datasets. The NIS database has the following unique merits: (1) it is one of the largest databases in the United States and may therefore represent the true diversity of the population allowing for study of relatively rare conditions such as Crohn's disease and UC; (2) the NIS dataset includes several clinical and demographic variables that have ICD-9 diagnostic codes and that were reported by physicians during admission or upon

discharge, hence, providing information on risk factors not included in previous studies; and (3) underrepresentation/under-reporting for some of the variables of interest may be assumed to be equally distributed among groups and, therefore, associations are still valid.

However, certain limitations were also observed in this study. Although using a national database that identified specific ICD-9 diagnostic codes for premature delivery and SGA, it is difficult to account for variability in the diagnostic practices of physicians. In addition, the study was limited by the inability to identify some demographic characteristics such as socioeconomic status, which was shown to associate with SGA and prematurity.³⁷ То overcome such limitation, we controlled for type of insurance as an indirect indicator for socioeconomic status. As HCUP data is a de-identified dataset, we could not link between the babies' records and those of their mothers. However, all relevant maternal conditions (including IBD subtypes) are provided as ICD9 codes, along with several factors related to their offspring such as prematurity and small for gestational age. Data about dietary behaviors. level of education. or psychological confounders were not documented and could not be controlled for in the logistic regression models. The difficulty in assessment is further compounded by the fact that many of the medications used to treat IBD could be associated with preterm delivery,¹⁸ although it is believed that the greatest risk to adverse outcomes is due to active disease and not active therapy.¹⁹ Furthermore, using ICD codes to assess for the presence of Crohn's disease or UC did not allow us access to information

about disease activity during pregnancy. Any active inflammation during pregnancy can be associated with negative birth outcomes. Disease activity may be confounded by medication use, race/ethnicity and other unknown confounders. Finally, we could not explain the higher prevalence of alcohol and drug use among pregnant women with IBD in this sample. These findings may be the result of surveillance bias, or it may be that such diseases may be accompanied by mental health disorders and vulnerability to addiction.

Conclusion

This study supported the assertion that IBD was associated with preterm and SGA birth; however, risk disparities existed among race/ethnic groups and IBD subtypes. These findings could be a valuable resource for clinicians while counseling pregnant women about differences in race/ethnicity and IBD subtype. Further qualitative studies are warranted to explain variability of outcomes across different race/ethnic subgroups.

References

 Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology. 2004 May;126(6):1504-17. <u>https://doi.org/10.1053/j.gastro.2004.01.</u> 063 PMID: 15168363.

- Kappelman MD, Rifas-Shiman SL, Kleinman K, Ollendorf D, Bousvaros A, Grand RJ, Finkelstein JA. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. Clin Gastroenterol Hepatol. 2007 Dec;5(12):1424-9. <u>https://doi.org/10.1016/j.cgh.2007.07.01</u>
 Epub 2007 Sep 29. PMID: 17904915.
- Bernstein CN, Shanahan F. Disorders of a modern lifestyle: reconciling the epidemiology of inflammatory bowel diseases. Gut. 2008 Sep;57(9):1185-91. <u>https://doi.org/10.1136/gut.2007.122143</u> Epub 2008 May 30. PMID: 18515412.
- Goh K, Xiao SD. Inflammatory bowel disease: a survey of the epidemiology in Asia. J Dig Dis. 2009 Feb;10(1):1-6. <u>https://doi.org/10.1111/j.1751-</u> <u>2980.2008.00355.x</u> PMID: 19236540.
- Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012 Jan;142(1):46-54.e42; quiz e30. https://doi.org/10.1053/j.gastro.2011.10. 001 Epub 2011 Oct 14. PMID: 22001864.
- 6. Chouraki V, Savoye G, Dauchet L, Vernier-Massouille G, Dupas JL, Merle V, Laberenne JE, Salomez JL, Lerebours E, Turck D, Cortot A, Gower-Rousseau C, Colombel JF. The changing pattern of Crohn's disease incidence in northern France: a continuing increase in the 10to 19-year-old age bracket (1988-2007). Pharmacol Ther. Aliment 2011 May;33(10):1133-42. https://doi.org/10.1111/i.1365-2036.2011.04628.x. Epub 2011 Mar 16. PMID: 21488915.
- Kornfeld D, Cnattingius S, Ekbom A. Pregnancy outcomes in women with inflammatory bowel disease--a population-based cohort study. Am J Obstet Gynecol. 1997 Oct;177(4):942-6. <u>https://doi.org/10.1016/S0002-</u> <u>9378(97)70298-9</u> PMID: 9369849.

- Molnár T, Farkas K, Nagy F, Lakatos PL, Miheller P, Nyári T, Horváth G, Szepes Z, Marik A, Wittmann T. Pregnancy outcome in patients with inflammatory bowel disease according to the activity of the disease and the medical treatment: a case-control study. Scand J Gastroenterol. 2010 Nov;45(11):1302-6. <u>https://doi.org/10.3109/00365521.2010.</u> <u>503967</u> Epub 2010 Jul 5. PMID: 20602569.
- Fonager K, Sørensen HT, Olsen J, Dahlerup JF, Rasmussen SN. Pregnancy outcome for women with Crohn's disease: a follow-up study based on linkage between national registries. Am J Gastroenterol. 1998 Dec;93(12):2426-30. <u>https://doi.org/10.1111/j.1572-</u> 0241.1998.00698.x PMID: 9860403.
- 10. Dominitz JA, Young JC, Boyko EJ. Outcomes of infants born to mothers with inflammatory bowel disease: a population-based cohort study. Am J Gastroenterol. 2002 Mar;97(3):641-8. <u>https://doi.org/10.1111/j.1572-</u> 0241.2002.05543.x. PMID: 11926208.
- Nørgård B, Fonager K, Sørensen HT, Olsen J. Birth outcomes of women with ulcerative colitis: a nationwide Danish cohort study. Am J Gastroenterol. 2000 Nov;95(11):3165-70. <u>https://doi.org/10.1111/j.1572-</u> 0241.2000.03290.x PMID: 11095336.
- 12. Porter RJ, Stirrat GM. The effects of inflammatory bowel disease on pregnancy: a case-controlled retrospective analysis. Br J Obstet Gynaecol. 1986 Nov;93(11):1124-31. <u>https://doi.org/10.1111/j.1471-</u> 0528.1986.tb08632.x PMID: 3778845.
- Getahun D, Fassett MJ, Longstreth GF, Koebnick C, Langer-Gould AM, Strickland D, Jacobsen SJ. Association between maternal inflammatory bowel disease and adverse perinatal outcomes. J Perinatol. 2014 Jun;34(6):435-40. <u>https://doi.org/10.1038/jp.2014.41</u> Epub 2014 Mar 20. PMID: 24651735.

- 15. Mahadevan U, Robinson C, Bernasko N, Boland B. Chambers C. Dubinsky M. Friedman S, Kane S, Manthey J, Sauberan J, Stone J, Jain R. Inflammatory Bowel Disease in Pregnancy Clinical Care Pathway: A Report from the American Gastroenterological Association IBD Parenthood Project Working Group. Gynecol. Am Obstet 2019 .1 Apr;220(4):308-323. https://doi.org/10.1016/j.ajog.2019.02.02

<u>7</u> PMID: 30948039.

- Nguyen GC, Boudreau H, Harris ML, Maxwell CV. Outcomes of obstetric hospitalizations among women with inflammatory bowel disease in the United States. Clin Gastroenterol Hepatol. 2009 Mar;7(3):329-34. <u>https://doi.org/10.1016/j.cgh.2008.10.02</u> <u>2</u> Epub 2008 Oct 30. PMID: 19027089.
- Cornish J, Tan E, Teare J, Teoh TG, Rai R, Clark SK, Tekkis PP. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. Gut. 2007 Jun;56(6):830-7. <u>https://doi.org/10.1136/gut.2006.108324</u> Epub 2006 Dec 21. PMID: 17185356; PMCID: PMC1954859.
- Wispelwey BP, Sheiner E. Inflammatory bowel disease and preterm delivery. Arch Gynecol Obstet. 2013 Oct;288(4):725-30. <u>https://doi.org/10.1007/s00404-013-2989-3</u> Epub 2013 Aug 10. PMID: 23934241.

- Beaulieu DB, Kane S. Inflammatory bowel disease in pregnancy. World J Gastroenterol. 2011 Jun 14;17(22):2696-701. <u>https://doi.org/10.3748/wjg.v17.i22.2696</u> PMID: 21734776; PMCID: PMC3122257.
- 20. HCUP Nationwide Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP). 1993-2008. Agency for Healthcare Research and Quality, Rockville, MD. <u>www.hcup-</u> <u>us.ahrq.gov/overview.jsp</u> Accessed on 1 August 2015
- 21. The Center for Disease Control and Prevention. (2013) Preterm birth. Available at: http://www.cdc.gov/reproductivehealth/ maternalinfanthealth/pretermbirth.htm. Accessed on 28 February 2015
- 22. U.S. National Library of Medicine. Small for Gestational Age. Available at: http://www.nlm.nih.gov/medlineplus/enc y/article/002302.htm. Accessed on 6 August 2015
- 23. Bortoli A, Pedersen N, Duricova D, D'Inca R, Gionchetti P, Panelli MR, Ardizzone S, Sanroman AL, Gisbert JP, Arena I, Riegler G, Marrollo M, Valpiani D, Corbellini A, Segato S, Castiglione F, Munkholm P; European Crohn-Colitis Organisation (ECCO) Study Group of Epidemiologic Committee (EpiCom). Pregnancy outcome in inflammatory bowel disease: prospective European case-control ECCO-EpiCom studv. 2003-2006. Aliment Pharmacol Ther. Oct:34(7):724-34. 2011 https://doi.org/10.1111/i.1365-2036.2011.04794.x Epub 2011 Aug 4. Erratum in: Aliment Pharmacol Ther.

2013 Aug;38(3):328. PMID: 21815900.

- Stephansson O, Larsson H, Pedersen L, Kieler H, Granath F, Ludvigsson JF, Falconer H, Ekbom A, Sørensen HT, Nørgaard M. Congenital abnormalities and other birth outcomes in children born to women with ulcerative colitis in Denmark and Sweden. Inflamm Bowel Dis. 2011 Mar;17(3):795-801. <u>https://doi.org/10.1002/ibd.21369</u> PMID: 20564537.
- 26. Stephansson O, Larsson H, Pedersen L, Kieler H, Granath F, Ludvigsson JF, Falconer H, Ekbom A, Sørensen HT, Nørgaard M. Crohn's disease is a risk factor for preterm birth. Clin Gastroenterol Hepatol. 2010 Jun;8(6):509-15 <u>https://doi.org/10.1016/j.cgh.2010.02.01</u> <u>4</u> Epub 2010 Mar 2. PMID: 20202483.
- Logan RF, Kay CR. Oral contraception, smoking and inflammatory bowel disease--findings in the Royal College of General Practitioners Oral Contraception Study. Int J Epidemiol. 1989 Mar;18(1):105-7. <u>https://doi.org/10.1093/ije/18.1.105</u> PMID: 2722351.
- Vessey M, Jewell D, Smith A, Yeates D, McPherson K. Chronic inflammatory bowel disease, cigarette smoking, and use of oral contraceptives: findings in a large cohort study of women of childbearing age. Br Med J (Clin Res Ed). 1986 Apr 26;292(6528):1101-3. <u>https://doi.org/10.1136/bmj.292.6528.11</u> 01 PMID: 3084016; PMCID: PMC1340036.

- 29. Savoye G. Is preterm delivery in inflammatory bowel disease women part of the burden of innate immunity deficiency? Am J Gastroenterol. 2010 Feb;105(2):473-4. https://doi.org/10.1038/ajg.2009.551. PMID: 20139886.
- 30. Hermon-Taylor J. Protagonist. Mycobacterium avium subspecies paratuberculosis is a cause of Crohn's disease. Gut. 2001 Dec;49(6):755-6. <u>https://doi.org/10.1136/gut.49.6.755</u> PMID: 11709506; PMCID: PMC1728545.
- Reddy D, Murphy SJ, Kane SV, Present DH, Kornbluth AA. Relapses of inflammatory bowel disease during pregnancy: in-hospital management and birth outcomes. Am J Gastroenterol. 2008 May;103(5):1203-9. <u>https://doi.org/10.1111/j.1572-</u> 0241.2007.01756.x Epub 2008 Apr 16. PMID: 18422816.
- 32. Ekbom A, Daszak P, Kraaz W, Wakefield AJ. Crohn's disease after in-utero measles virus exposure. Lancet. 1996 Aug 24;348(9026):515-7. <u>https://doi.org/10.1016/S0140-</u> <u>6736(96)04429-7</u> PMID: 8757154.
- 33. Klement E, Cohen RV, Boxman J, Joseph A, Reif S. Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis. Am J Clin Nutr. 2004 Nov;80(5):1342-52. <u>https://doi.org/10.1093/ajcn/80.5.1342</u> PMID: 15531685.
- 34. Nasef NA, Ferguson LR. Inflammatory bowel disease and pregnancy: overlapping pathways. Transl Res. 2012 Jul;160(1):65-83. <u>https://doi.org/10.1016/j.trsl.2011.12.002</u> Epub 2011 Dec 23. PMID: 22687963.
- 35. Das KM. Relationship of extraintestinal involvements in inflammatory bowel disease: new insights into autoimmune pathogenesis. Dig Dis Sci. 1999 Jan;44(1):1-13. https://doi.org/10.1023/A:102662952823
 <u>3</u> PMID: 9952216.

- 36. Turkcapar N, Toruner M, Soykan I, Aydintug OT, Cetinkaya H, Duzgun N, Ozden A, Duman M. The prevalence of extraintestinal manifestations and HLA association in patients with inflammatory bowel disease. Rheumatol Int. 2006 May;26(7):663-8 <u>https://doi.org/10.1007/s00296-005-</u>0044-9 Epub 2005 Sep 1. PMID: 16136311.
- 37. Mortensen LH. Socioeconomic inequality in birth weight and gestational age in Denmark 1996-2007: using a familybased approach to explore alternative explanations. Soc Sci Med. 2013 Jan;76(1):1-7. <u>https://doi.org/10.1016/j.socscimed.2012</u> <u>.08.021</u>. Epub 2012 Sep 11. PMID: 23026073.
- Heaman M, Kingston D, Chalmers B, Sauve R, Lee L, Young D. Risk factors for preterm birth and small-forgestational-age births among Canadian women. Paediatr Perinat Epidemiol. 2013 Jan;27(1):54-61. <u>https://doi.org/10.1111/ppe.12016</u> PMID: 23215712.