ORIGINAL ARTICLE

Inflammatory bowel disease and new-onset psychiatric disorders in pregnancy and post partum: a population-based cohort study

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ABSTRACT

Objective Patients with inflammatory bowel disease (IBD) have an elevated risk of mental illness. We determined the incidence and correlates of new-onset mental illness associated with IBD during pregnancy and post partum.

Design This cohort study using population-based health administrative data included all women with a singleton live birth in Ontario, Canada (2002–2014). The incidence of new-onset mental illness from conception to 1-year post partum was compared between 3721 women with and 798 908 without IBD, generating adjusted HRs (aHR). Logistic regression was used to identify correlates of new-onset mental illness in the IBD group.

Results About 22.7% of women with IBD had new-onset mental illness versus 20.4% without, corresponding to incidence rates of 150.2 and 132.8 per 1000 patient-years (aHR 1.12, 95% CI 1.05 to 1.20), or one extra case of new-onset mental illness per 43 pregnant women with IBD. The risk was elevated in the post partum (aHR 1.20, 95% CI 1.09 to 1.31), but not during pregnancy, and for Crohn's disease (aHR 1.12, 95% CI 1.02 to 1.23), but not ulcerative colitis. The risk was specifically elevated for a new-onset mood or anxiety disorder (aHR 1.14, 95% CI 1.04 to 1.26) and alcohol or substance use disorders (aHR 2.73, 95% CI 1.42 to 5.26). Predictors of a mental illness diagnosis were maternal age, delivery year, medical comorbidity, number of prenatal visits, family physician obstetrical care and infant mortality.

Conclusion Women with IBD were at an increased risk of new-onset psychiatric diagnosis in the postpartum period, but not during pregnancy. Providers should look to increase opportunities for prevention, early identification and treatment accordingly.

Significance of this study

What is already known about this subject?

- Inflammation is associated with psychiatric disorders.
- Inflammatory bowel disease (IBD) is linked to elevated risk for mental illness, especially when inflammation is active.
- Pregnancy is a state of altered immune functioning, which may lead to an increased risk of depression and anxiety perinatally in otherwise healthy women.

What are the new findings?

- Women with IBD are at an elevated risk of new-onset perinatal mental illness, especially mood and anxiety disorders and substance use disorders.
- The elevated risk appears to be in the postpartum period, not in pregnancy, and to be in women with Crohn's disease, but not ulcerative colitis.
- Correlates of postpartum mental illness among women with IBD are maternal age, year of delivery, medical comorbidity, infant mortality, and the frequency and nature of prenatal care.

How might it impact on clinical practice in the foreseeable future?

- Healthcare providers, including gastroenterologists and obstetricians, should be aware of the elevated risk of anxiety, depression and substance use disorders in postpartum women with IBD.
- Screening tools to identify psychiatric disorders in people with IBD should be validated in perinatal women.
- Pregnant and postpartum women with IBD who are at risk for or show symptoms of perinatal mental illness should be promptly referred for mental healthcare.

BACKGROUND

Inflammation is associated with the onset of psychiatric disorders outside the context of pregnancy and childbirth.[1] Proinflammatory cytokines and other inflammatory biomarkers are associated with depression and anxiety.[2 3] Pregnancy is an altered state of immune functioning, so inflammatory processes may play a role in the onset of psychiatric disorders in pregnancy and post partum. Several immune-related disorders, including pre-eclampsia and gestational diabetes, are associated with an increased risk for psychiatric disorders in pregnancy and post partum.[4 5]

Inflammatory bowel disease (IBD) is a chronic immune-mediated disease of the gastrointestinal system and consists of two main types, Crohn's

disease (CD) and ulcerative colitis (UC). Its peak onset occurs in the second or third decades of life.[6] Therefore, many reproductive-age women are affected. While some women with IBD experience a quiescence of disease in pregnancy, a subset experience relapsing illness, in particular in the weeks and months after delivery.[7] Active IBD in pregnancy is associated with increased risk for several adverse perinatal outcomes, including fetal growth restriction, preterm birth and fetal loss.[8 9] Importantly, inflammation of IBD affects not only the gastrointestinal tract but also other organs such as bone and brain.[10 11] A large body of literature documents an increased prevalence of mental illness, primarily anxiety and depression, in non-pregnant individuals with IBD, possibly due to the effect of pro-inflammatory cytokines or the stress of managing a chronic disease.[12]

The primary objective of this study was to evaluate the relationship between IBD and new-onset mental illness in a population-based Canadian sample of pregnant and postpartum women. A secondary objective was to identify sociodemographic and clinical correlates of risk among women with IBD.

METHODS

Study design, setting and data sources

This population-based cohort study used health administrative data from 2002 to 2015 in Ontario, Canada (13.4 million people, 38% of the Canadian population).[13] Ontario collects health administrative data on all legal residents who qualify for universal single-payer healthcare (>99% of the population). Data are maintained by a health data repository, ICES, via an agreement with the Ontario Ministry of Health and Long-Term Care, with the data available to researchers in uncleaned and unedited format.[14] Multiple databases are linked using a unique encrypted identification number based on the Ontario health card number assigned to each Ontario resident.

We used the followed databases for the current study: (1) Registered Persons Database (RPDB) that includes date of birth, postal code of residence and updated information on vital status and migration out of Ontario; (2) Ontario Health Insurance Plan (OHIP) data that include physician billing data since 1991 using a simplified three-digit version of the International Classification of Diseases, Ninth Revision (ICD-9); (3) National Ambulatory Care Reporting System for emergency department (ED) visits from 2002 onward using the ICD-10 classification system; (4) Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) containing medical hospitalisations since 1988 and mental health hospitalisations from 1988 to 2005 using the ICD-10 classification system from 2002 onward; and (5) Ontario Crohn's and Colitis Cohort, which contains all patients diagnosed with IBD living in Ontario from 1991 onward, with incident cases identified after 1994 (for paediatric-onset IBD) or 1999 (for adult-onset IBD) using validated algorithms based on health services utilisation[15 16]; (6) Ontario Mental Health Reporting System (OMHRS) which contains information on all inpatient psychiatric hospitalisations since 2005 with diagnoses recorded using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnostic system; (7) ICES Physician Database (IPDB) to establish specialty of the physician providing obstetrical care based on board certification and practice pattern. We established the estimated date of conception based on the infant's gestational age at birth recorded in the MOMBABY datafile that uses information from CIHI-DAD and links the health records of mothers with those of their newborns for all Ontario hospital births (>98% of births in Ontario).[17] Data in these registers, including billing claims for physician services, demographics and primary inpatient diagnoses, are reliable and complete.[18 19]

Population

All Ontario women with a prepregnancy diagnosis of IBD, without a history of a psychiatric disorder and with an inhospital delivery of a live singleton infant, where the earliest estimated date of conception was 1 April 2002 and the latest delivery date was 31 March 2015, were considered for inclusion. We excluded records in which the mother's and infant's data could not be linked and women with interrupted healthcare eligibility. As the objective of the study was to determine the risk for a new psychiatric disorder, we also excluded women who had been diagnosed with a psychiatric disorder anytime between database inception and the date of conception, using outpatient physician billing data as follows: (1) psychotic disorder, using a validated algorithm requiring one hospitalisation or three outpatient visits associated with a diagnosis of schizophrenia and related psychotic disorders (CIHI-DAD: ICD10: F20, F25, F29; OHIP diagnostic codes 295 or 298) within a 3-year period[20]; or (2) mood, anxiety and related disorders, using a validated algorithm requiring five visits for any other psychiatric diagnosis (OHIP diagnostic codes: 290–318, excluding 295 and 298) within a 2-year period.[21] We also excluded women who additionally had a history of hospitalisation or ED visit for any psychiatric disorder or self-induced harm event (hospitalisation ICD-10: F00-F99; ED visit ICD-10: F00-F99, X60-X84, Y10-Y19, Y28).

We classified women as having or not having IBD based on validated algorithms. These algorithms accurately identified children <18 years with incident IBD with the following diagnostic accuracies: sensitivity 89.6%–91.1%, specificity 99.5%–100%, positive predictive value (PPV) 59.2%–76.0% and negative predictive value (NPV) 99.9%–100%.[15] The algorithms identified adult-onset IBD with the following diagnostic accuracies: sensitivity 76.8%, specificity 96.2%, PPV 81.4% and NPV 95.0%.[16] To be classified into the IBD exposed group, a pregnant woman had to have been diagnosed with IBD at least 1 year prior to pregnancy. A validated look-back period was used to distinguish incident from prevalent cases with an accuracy of 95%.[15 16] A validated algorithm was used to classify IBD as being CD or UC based on the diagnoses assigned at the latest five of nine outpatient physician visits, which accurately assigned IBD type in 91.1% of cases.[16] Women diagnosed with IBD after conception were excluded from the cohort. All other women acted as the unexposed population. For women with multiple deliveries during the study period, we randomly selected one pregnancy for inclusion. If a woman became pregnant before and after IBD diagnosis, we selected the pregnancy after IBD diagnosis and excluded the preceding pregnancy.

Outcomes

The main outcome of interest was a perinatal psychiatric disorder, defined as a psychiatric disorder diagnosed during pregnancy (between the estimated date of conception and delivery) or within the first year post partum. Diagnoses were obtained from physician billing codes (OHIP codes 290–318 by a psychiatrist or family physician, the latter using a validated algorithm which identified mental health visits with a sensitivity of 80.7%, specificity 97.0%, (PPV 84.9%, NPV 96.0%,[22] as well as from ED visits (NACRS, ICD-10 F00-F99) and inpatient hospitalisations (CIHI-DAD, ICD-10 F00-F99 or OMHRS, any DSM-IV diagnosis) where diagnostic coding is entered by professional coders, is quality controlled and is 85%–95% accurate.[23] See the online

supplemental table 1 for the full list of codes used to define the outcomes. We further divided perinatal psychiatric episodes into onset in pregnancy (divided into trimesters) or the first 365 days post partum, divided into early post partum (within the first 90 days following delivery) and late (91 to 365 days post partum), as the first 3 months following childbirth have been associated with the highest lifetime risk of first-onset psychiatric episodes.[24] We also measured the main and subdivided outcomes by category of psychiatric diagnosis: (1) psychotic disorders (eg, schizophrenia and related disorders); (2) mood and anxiety disorders (also including related disorders such as obsessive-compulsive disorder and post-traumatic stress disorder; (3) substance and alcohol use disorders; and (4) other psychiatric diagnoses (online supplemental table 1).[25] To assess the severity of illness during the perinatal period, we also measured the type of contact (inpatient, ED or outpatient).

Covariates

A range of covariates was included in the analyses to identify the specific contribution of IBD to the main outcome and to explore factors that could be associated with the outcome among women with IBD. Sociodemographic variables included maternal age, neighbourhood income quintile (a validated proxy for individual-level income[26]) and rural/urban residence. Maternal medical comorbidities predating the pregnancy were determined using the Johns Hopkins Collapsed Adjusted Diagnostic Groups (CADG).[27] The physician who provided the majority (>75%) of prenatal obstetrical care was classified as being: (1) general practitioner/family physician (GP/FP); (2) obstetrician; or (3) shared care between GP/FP and obstetrician. An additional category of inadequate prenatal care (<4 prenatal physician visits) was also included. Maternal and infant health variables were gestational diabetes, pregnancy-induced hypertension and specific pregnancy and infant outcomes, including preterm birth, fetal growth abnormalities and severe neonatal morbidity defined by a neonatal intensive care unit (NICU) admission.[28] A full list of codes used to define maternal, pregnancy and neonatal characteristics is available in the online supplemental table 2.

Statistical analysis

The distribution of covariates was described for each group using means (with SD), medians (with IQR) or proportions, where appropriate.

For the main outcome, we calculated the incidence of perinatal mental illness per 1000 person-years at risk for women with and without IBD. We used multivariable Cox proportional hazard models to generate crude and adjusted HRs (HR) and 95% CIs to compare women with versus without IBD. HRs were adjusted for maternal age at delivery, calendar year of delivery, income, rural/urban residence and prenatal or perinatal care variables that differed substantially between groups and could be related to the likelihood that a woman might have, or be identified as having, perinatal mental illness: prenatal ultrasound under 20 weeks (yes/no), number of prenatal visits and caesarean section (C-section) delivery. Secondary outcomes (ie, category of a psychiatric episode, timing of episode and so on) were adjusted for the same set of variables. Subgroup analysis stratified women with IBD by type of IBD: CD or UC. For this analysis, we excluded women with IBD type unclassifiable (for whom the classification algorithm could not determine whether CD or UC).

Among women with IBD, we built regression models to identify covariates independently associated with first-onset perinatal psychiatric episodes. Univariate analysis using logistic regression was used to determine the crude association between each covariate and outcome. All variables with p<0.20 in univariate analysis were assessed for collinearity (variance inflation factor (VIF) >4) to select an initial set of variables for the multivariable model. Using a backwards selection process, we then entered all of these variables into the model, dropped variables when there were high levels of interaction (>0.80 based on polychromic correlations) and collinearity (VIF >4), and retained all variables significant at p<0.05 in the final model. Previous hospitalisation for IBD (yes/no) was left in the final models despite non-significance because of its importance as a proxy for pre-pregnancy disease severity and because there was a trend toward significance (p<0.10).

All statistical analysis was conducted using SAS V.9.3. P values <0.05 were considered statistically significant.

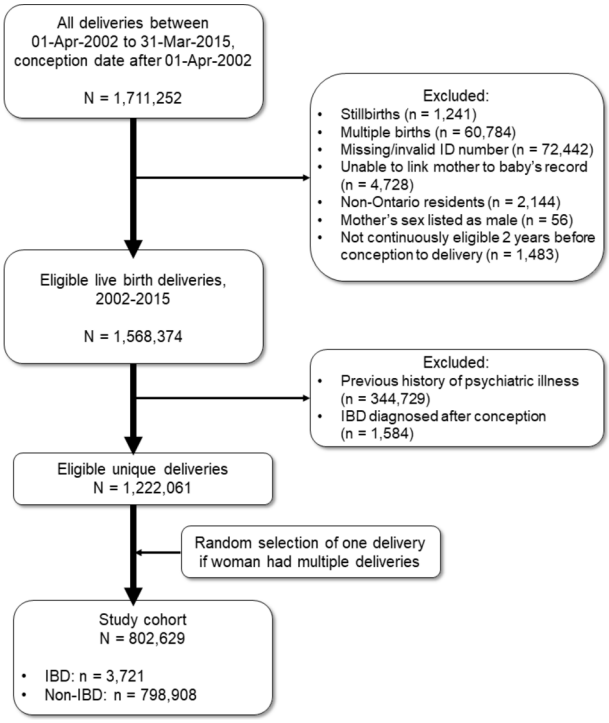

Figure 1 Study flow diagram. IBD, inflammatory bowel disease.

RESULTS

Descriptive characteristics

From 1 568 374 live births, 344 729 (22.0%) were excluded due to a prior history of mental illness in the mother, and 1584 (0.1%) were excluded because of maternal diagnosis with IBD between conception and delivery, leaving 1 222 061 deliveries to 802 629 unique women where 1 pregnancy was randomly selected per woman for analysis (figure 1).

Women with IBD (n=3721) were slightly older at delivery than women without IBD (n=798 908)(31.6±4.6 y vs 30.3±5.5 years)(table 1). They were more likely to live in the highest income neighbourhoods (Quintiles 4 or 5: 47.1% vs 36.4%) and to live in rural communities (12.4% vs 9.2%). They were more slightly more likely to receive care by an obstetrician during pregnancy (39.1% vs 35.4%) and had more prenatal ultrasounds (mean ±SD: 7.8±4.9 vs 6.6±4.3) and prenatal visits (15.0±5.4 vs. 14.2±5.6, p<0.001). They were slightly less likely to have gestational diabetes (4.6% vs 5.7%,), but not pre-eclampsia (1.5% vs 1.2%) or gestational hypertension (2.1%

Table 1 Descriptive characteristics of the cohort presented as N(%) unless otherwise specified

	IBD (n=3721)	No IBD (n=798 908)
Maternal characteristics		
Mean (SD) maternal age at delivery in years	31.6 (4.6)	30.3 (5.5)
Primiparous	1803 (48.5)	401 467 (50.3)
Income quintile		
Q1 (lowest)	484 (13.0)	179 404 (22.5)
Q2	642 (17.3)	161 548 (20.2)
Q3	832 (22.4)	162 570 (20.3)
Q4	919 (24.7)	163 940 (20.5)
Q5 (highest)	835 (22.4)	128 091 (16.0)
Missing	9 (0.2)	3355 (0.4)
Rural region of residence	462 (12.4)	73 585 (9.2)
Pre-pregnancy medical characteristics		
Diabetes	50 (1.3)	10 936 (1.4)
Hypertension	85 (2.3)	16 461 (2.1)
Number of major CADGs		
0	1586 (42.6)	713 488 (89.3)
1	1621 (43.6)	74 921 (9.4)
2	438 (11.8)	9380 (1.2)
3	69 (1.9)	1011 (0.1)
4	7 (0.2)	101 (0.0)
5	0 (0)	7 (<0.1)
Previous hospital admission for IBD (ever)	870 (23.4)	0 (0)
Care by a gastroenterologist	2377 (63.9)	390 (0.05)
Prenatal care		
Had a prenatal ultrasound	3704 (99.5)	787 066 (98.5)
Ultrasound before 20 weeks GA	3528 (94.8)	715 254 (89.5)
Mean number of ultrasounds during pregnancy (SD)	7.84 (4.90)	6.62 (4.30)
Mean number of prenatal visits (SD)	14.97 (5.42)	14.19 (5.65)
Type of physician providing prenatal care		
<4 visits	136 (3.7)	44 915 (5.6)
General practitioner/family physician only	538 (14.5)	130 445 (16.3)
Obstetrician only	1456 (39.1)	282 495 (35.4)
Shared care	1591 (42.8)	341 053 (42.7)
Care by a gastroenterologist during pregnancy	2635 (70.8)	506 (0.1)
Pregnancy and delivery complications and characteristics		
Gestational diabetes	170 (4.6)	45 812 (5.7)
Gestational hypertension	80 (2.1)	20 505 (2.6)
Pre-eclampsia	55 (1.5)	9919 (1.2)
Labour induction	880 (23.6)	176 943 (22.1)
Caesarean section delivery	1312 (35.3)	224 169 (28.1)
Operative vaginal delivery	374 (10.1)	88 732 (11.1)
Major perineal trauma	279 (7.5)	66 395 (8.3)
Offspring characteristics		
Sex, female	1750 (47.0)	385 010 (48.2)
Premature birth	309 (8.3)	48 855 (6.1)
Mean birth weight (SD)	3341.15 (564.27)	3380.21 (554.60)
Small for GA	515 (13.8)	130 544 (16.3)
Large for GA	439 (11.8)	118 643 (14.9)
Neonatal mortality	6 (0.2)	1341 (0.2)
Infant mortality	8 (0.2)	1903 (0.2)
Respiratory distress syndrome	62 (1.7)	8393 (1.1)
Seizure	6 (0.2)	1250 (0.2)
Sepsis	35 (0.9)	5684 (0.7)
Intraventricular haemorrhage	18 (0.5)	2777 (0.3)
Persistent fetal circulation	≤5 (<0.1)	1236 (0.2)
Neonatal abstinence syndrome	6 (0.2)	532 (0.1)
Admission to special care unit	10 (0.3)	2126 (0.3)
Congenital anomalies	27 (0.7)	4533 (0.6)

CADG, collapsed adjusted diagnostic groups; GA, gestational age; IBD, inflammatory bowel disease; Q, quintile.

vs 2.6%). They were more likely to deliver by C-section (35.3% vs 28.1%,), and their infants were more likely to be born preterm (8.3% vs 6.1%), but not small (13.8% vs 16.3%) or large (11.8% vs 14.9%) for gestational age. The infants were statistically more likely to experience respiratory distress syndrome (1.7% vs 1.1%) and neonatal abstinence syndrome (0.2% vs 0.1%). Risks for neonatal seizure, sepsis, intraventricular haemorrhage, congenital anomaly, congenital/neonatal infection and mortality were similar between groups.

Incidence of perinatal mental illness

Perinatal mental illness affected 22.7% of women with IBD and 20.4%. of women without IBD, corresponding to an incidence of 150.2 per 1000 person-years for women with IBD and 132.8 per 1000 person-years among women without, a crude HR of 1.13 (95% CI 1.06 to 1.21) and adjusted HR (aHR) of 1.12 (1.05 to 1.20) (table 2). Risk was increased for women with IBD in the postpartum period (aHR 1.20, 95% CI 1.09 to 1.31), but not during pregnancy (aHR 1.04, 95% CI 0.94 to 1.15). The HRs were higher in the early postpartum period, 0–90 days post partum (aHR 1.29, 95% CI 1.14 to 1.47) than in the later postpartum period, 91–365 days post partum (aHR 1.14, 95% CI 1.003 to 1.29).

Subgroup analyses by type of IBD showed the same patterns as in the overall analysis among women with CD, but there was no increased risk overall or at specific time points for women with UC (online supplemental table 3).

Diagnosis and severity of presentation

Compared to women without IBD, women with IBD were at increased risk for 2 of the 4 mental illness diagnostic categories: (1) mood and anxiety disorders (aHR 1.13, 95% CI 1.05 to 1.22) and (2) alcohol and substance use disorders (aHR 1.86, 95% CI 1.03 to 3.36). There was no evidence of increased risk for psychotic disorders (HR 0.20, 95% CI 0.03 to 1.43) or for other diagnoses (HR 1.05, 95% CI 0.87 to 1.27) (table 3). Diagnoses mainly occurred in the outpatient setting, and this is where the increased risk for a new-onset perinatal mental illness among women with IBD was observed (aHR 1.12, 95% CI 1.05 to 1.20). There was no increased risk for presentation to the emergency department or for inpatient psychiatric hospitalisation. In subgroup analysis, the same patterns of risk were found in CD, but not patients with UC (online supplemental table 3).

Prediction models

In women with IBD, we created two models to predict the risk of a perinatal psychiatric episode (see online supplemental table 4). The first model included only pre-pregnancy and pregnancy variables (figure 2A). For this model, maternal age category, prepregnancy IBD admission, delivery year, the number of prenatal visits and the specialty of the primary obstetrical care provider predicted the risk of a perinatal psychiatric episode. A second model (figure 2B) included postpartum predictive variables,

Table 2 Proportion of women with new-onset mental illness in the perinatal period, with incidence rates overall, and by timing of diagnosis, comparing 3721 women with and 798 908 without IBD

	Groups	N (%) with new-onset perinatal mental illness	Incidence per 1000 PYs	Crude HR (95% CI)	Adjusted HR* (95% CI)
Overall	No IBD	1 63 256 (20.4)	132.76	REF	REF
	IBD	846 (22.7)	150.17	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.20)
Pregnancy	No IBD	75 211 (9.4)	134.15	REF	REF
	IBD	371 (10.0)	143.58	1.07 (0.97 to 1.18)	1.04 (0.94 to 1.15)
Post partum	No IBD	88 045 (11.0)	72.84	REF	REF
	IBD	475 (12.8)	85.87	1.19 (1.08 to 1.30)	1.20 (1.09 to 1.31)
By trimester					
Trimester 1	No IBD	41 014 (5.1)	211.51	REF	REF
	IBD	206 (5.5)	228.97	1.09 (0.95,1.25)	1.05 (0.92 to 1.20)
Trimester 2	No IBD	21 348 (2.7)	56.93	REF	REF
	IBD	98 (2.6)	56.36	1.01 (0.83 to 1.23)	0.99 (0.81 to 1.20)
Trimester 3	No IBD	12 849 (1.6)	23.46	REF	REF
	IBD	67 (1.8)	26.55	1.14 (0.90 to 1.45)	1.15 (0.90 to 1.46)
Postpartum timing					
Early (0–90 days)	No IBD	39 878 (5.0)	55.98	REF	REF
	IBD	232 (6.2)	70.85	1.29 (1.14 to 1.47)	1.29 (1.13 to 1.47)
Late (91–365 days)	No IBD	48 167 (6.0)	41.00	REF	REF
	IBD	243 (6.5)	45.54	1.12 (0.98 to 1.27)	1.14 (1.003 to 1.29)

*Adjusted for maternal age at delivery, calendar year of delivery, income quintile, rural/urban residence, prenatal ultrasound <20 weeks (y/n), number of prenatal visits and caesarean section delivery.
IBD, inflammatory bowel disease; PY, person-years; REF, reference group;

and included severe neonatal morbidity and infant mortality as significant predictors of a perinatal psychiatric episode.

Due to the finding that women with IBD were at increased risk for a postpartum psychiatric episode, but were not at increased risk during pregnancy, we constructed a third predictive model including only psychiatric diagnoses in the postpartum period based on variables that were statistically significant in the online supplemental table 5. In this model (figure 2C), the following variables were significantly predictive: maternal age category, delivery year, CADG comorbidity score prior to pregnancy, number of prenatal visits, the specialty of the primary obstetrical care provider, and infant mortality.

DISCUSSION

Using a large, population-based cohort of women living in Ontario, Canada, we found women with IBD were at a small, but significantly increased risk for new-onset mental illness in the perinatal period compared with women without IBD. The increased risk was significant specifically in the postpartum

Table 3 Incidence and risk of perinatal mental illness among 3721 women with and 7 98 908 women without IBD based on mental illness diagnosis type, and severity (outpatient, emergency department and inpatient psychiatric care)

Outcome	Group	N (%)	Incidence per 1000 PYs	Crude HR (95% CI)	Adjusted HR (95% CI)
Type of contact					
Outpatient	No IBD	1 58 350 (19.8)	128.28	REF	REF
	IBD	825 (22.2)	145.85	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.20)
Inpatient hospitalisation	No IBD	406 (0.1)	0.29	REF	REF
	IBD	<6	0.15	0.53 (0.07 to 3.77)	0.65 (0.09 to 4.66)
Emergency department	No IBD	4500 (0.6)	3.24	REF	REF
	IBD	20 (0.5)	3.10	0.96 (0.62 to 1.49)	1.14 (0.73 to 1.79)
Diagnosis at first contact					
Psychotic disorder	No IBD	1130 (0.1)	0.81	REF	REF
	IBD	<6	0.15	0.19 (0.03 to 1.35)	0.20 (0.03 to 1.43)
Mood, anxiety and related disorders	No IBD	1 38 740 (17.4)	110.41	REF	REF
	IBD	727 (19.5)	126.11	1.14 (1.06 to 1.23)	1.13 (1.05 to 1.22)
Alcohol or substance use disorder	No IBD	1825 (0.2)	1.31	REF	REF
	IBD	11 (0.3)	1.70	1.30 (0.72 to 2.35)	1.86 (1.03 to 3.36)
Other	No IBD	21 561 (2.7)	15.74	REF	REF
	IBD	107 (2.9)	16.84	1.07 (0.89 to 1.29)	1.05 (0.87 to 1.27)

ED, emergency department; IBD, inflammatory bowel disease; PY, person-years; REF, reference group.

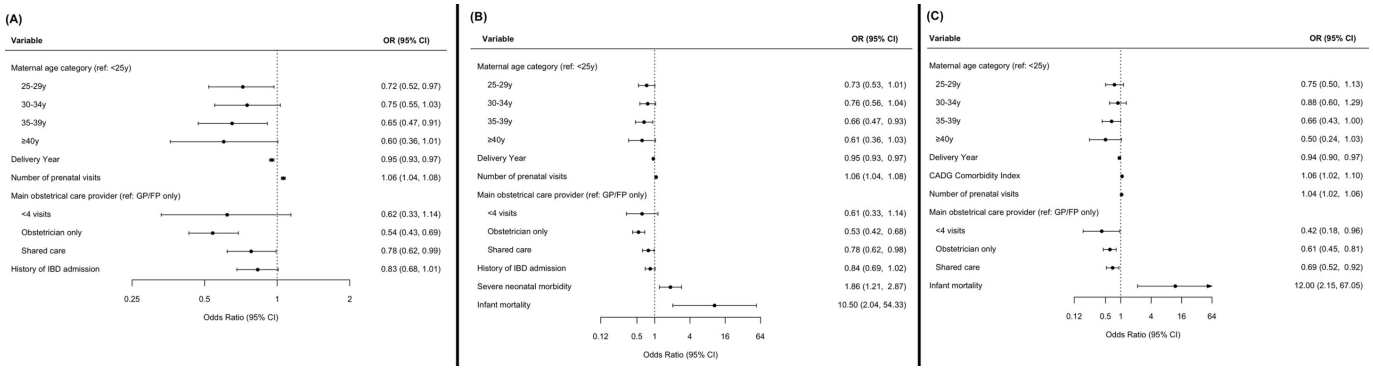

Figure 2 Multivariable predictive models for a perinatal psychiatric episode among pregnant women with IBD. (A) Pregnancy and postpartum psychiatric episode (model 1: excluding postnatal or infant variables). (B) Pregnancy and postpartum psychiatric episode (model 2: including postnatal and infant variables). (C) Postpartum psychiatric episode. NB. Models statistics are reported after removing variables that were no longer significant when included in the multivariable model (p>0.05). CADG, Johns Hopkins Collapsed Adjusted Diagnostic Groups; GP/FP, general practitioner/family physician; IBD, inflammatory bowel disease; REF, reference group; y, years.

period (especially the first 90 days post partum), and for two specific diagnostic subcategories: mood and anxiety disorders and substance-related disorders. Women with IBD were no more likely than women without IBD to be diagnosed with a psychotic disorder, nor to require a psychiatric ED visit or hospitalisation. Among women with IBD, factors associated with increased risk for being diagnosed with perinatal mental illness were demographics (maternal age, more distant year of delivery), clinical characteristics (greater likelihood with more medical comorbidities), the main prenatal care provider being a family physician, and infant morbidity and mortality. While the absolute increased risk for women with IBD is modest, given the substantive maternal and child morbidity (and sometimes mortality) associated with perinatal mental illness, any increased risk is potentially important at a health system level, especially if it could be prevented.

Context within existing literature

The rates of new-onset perinatal mental illness in this study, where it appears to be affecting one in five women overall are consistent with international estimates.[29] This level of morbidity is notable, especially considering that one in five pregnant women who had pre-existing mental illness were excluded from the cohort so not even included in these estimates. To our knowledge, this is the first study to demonstrate an increased risk for new-onset perinatal mental illness among women with IBD. The results are consistent with studies focused on non-pregnant individuals with IBD and in other immune-mediated inflammatory diseases such as multiple sclerosis and rheumatoid arthritis[30] where high rates of psychiatric illness, and in particular anxiety and depression, have been observed.[12 31–33] Our findings also align with those of a recent systematic review that found several other chronic medical illnesses (diabetes, heart disease, migraine and other neurological disorders) were associated with increased risk for depression in pregnancy and post partum.[34]

Most studies of the relationship between chronic medical illnesses and increased risk for psychiatric disorders have demonstrated an increased risk for non-psychotic mental disorders such as anxiety and depression. This has been observed both in perinatal and non-perinatal populations. The increased risk for perinatal depression and anxiety in the current study is consistent with those prior studies. However, the finding of an association between IBD and risk for a new-onset substance use disorder in the perinatal period is a novel one. While the diagnoses were rare (0.3% of women with IBD vs. 0.2% of women without IBD), the relative odds were 1.8-fold higher for IBD overall, and 2.7-fold higher in women with CD. This result, while it should be interpreted with caution as it is one of several secondary analyses, is consistent with population-based research in Manitoba, Canada (non-perinatal) demonstrating that patients with IBD were nearly three times more likely than controls to become heavy opioid users.[35]

Most predictors of a perinatal psychiatric disorder among women with IBD were similar to those seen outside this population, including young maternal age, infant morbidity and mortality, and also health service use that could increase the likelihood of detection of a psychiatric disorder (eg, more prenatal visits, receipt of obstetrical care from a family physician as opposed to an obstetrician).[36 37] Interestingly, having a prior admission for IBD reduced the likelihood of a perinatal psychiatric diagnosis, although this association was not statistically significant. If having a prior admission for IBD is indicative of the severity of IBD, these results would be inconsistent with those in studies of non-pregnant people with IBD, in which disease severity was associated with a greater risk for a psychiatric disorder and worse quality of life.[38–41] However, patients with IBD who had a history of more severe disease may have been more likely to be treated with immunomodulators and biologic therapies, which have been associated with lower risk of depression and improved health-related quality of life.[31 42 43]

Potential mechanisms

The mechanism that underlies the observed increased risk for perinatal mental illness may be multifactorial. Mental illness has been associated with inflammation and immune dysregulation.[44 45] Proinflammatory cytokines have been suggested to alter brain function and increase the risk of mental illness in patients with IBD.[46 47] Women with CD were specifically at increased risk for a perinatal mental disorder. CD is a disorder with a more systemic pattern of inflammation than UC, in which inflammation is more localised to the colon,[48 49] potentially explaining the higher risk for depression and anxiety. The finding that risk was elevated mostly in the early post partum would also be consistent with this, since that is the highest risk time for developing a mental illness during the perinatal period in general,[50] so perhaps there is a 'double vulnerability' for women with CD during this time. However, the risk for a substance use disorder was also elevated in CD, but not UC, and it is not clear that

systemic inflammation would be solely directly responsible for this. Rather, the relationship could be mediated through opioid use in response to pain that becomes chronic and develops into a substance use disorder. While the type of substance use disorder was not specified in our data, the increased rate of neonatal abstinence syndrome among infants of mothers with IBD (0.2% vs 0.1% of infants unexposed to IBD) suggests that this may be partly related to antenatal opioid use.

In addition to potential biological mechanisms at play, the transition to parenthood is also a psychological adjustment for many new mothers. Challenges include caring for a newborn, sleep deprivation and negotiating new roles within the context of the relationship with their partner. Life stressors have been repeatedly identified as predictors of increased risk for perinatal depressive and anxiety disorders,[36] and the burden of a chronic medical illness that may flare post partum could be construed in this manner.[7 51] The increased risk for perinatal mental illness was specific to the early postpartum (not antenatal) period, supporting this hypothesis. It is also possible that the increased risk observed in women with IBD could be due to their comfort with accessing the health system and better detection due to regular physician visits that occur because of their chronic disease.

Strengths and limitations

This study is strengthened by its large sample size and population-based cohort of women with and without IBD. Additionally, the ability to link mothers to their infants for hospital births allowed us to examine the role of both maternal and infant characteristics in predicting a perinatal psychiatric episode. As with all research using routinely collected health data,[52] this study has some essential limitations. First, the size of the cohort allowed for the statistical assessment of psychiatric illness rates while controlling for multiple confounders, but it also made the detection of small effects possible. While the absolute increased risk in women with IBD compared with controls was modest, the increase is still potentially important at a health system level, especially if it is preventable. Second, since we are identifying people with IBD and perinatal psychiatric episodes using health administrative data algorithms, there is a risk of misclassification of both exposure and outcome.[53] We used algorithms validated in Ontario for both health conditions, thereby minimising the risk. Mental illness diagnosed by non-physician healthcare providers (eg, psychologists and social workers) would not be contained within Ontario health administrative data, since these services are not funded by the government. We may be therefore be underestimating the incidence of mild mental illness. However, we have no reason to be believe that women with IBD are more or less likely than those without IBD to use non-government-funded services so there is unlikely to be a systematic bias at play that would influence the relative estimates (ie, the ORs and HRs reported in our study should be accurate, even if the crude incidence was underestimated for both groups). Third, there are potential confounders and potential mediators that we were unable to consider. No clinical data are available in these databases, and therefore we have no information on IBD phenotype, genotype, disease severity or quality of life. In particular, active inflammation cannot be measured with administrative data and may be associated with the risk of mental illness. Due to the lack of medication data, we could not assess the role of treatment on the incidence of psychiatric illness. For example, we were unable to determine the role that systemic corticosteroids may have played in the increased risk for psychiatric illness. Similarly, administrative data do not contain missing important disease characteristics of the psychiatric illness. We could not measure important predictors of psychiatric illness, such as psychosocial history, family history, marital status, education or perceived social support.

Implications and next steps

Our findings highlight that the well-described risk of psychiatric disease in people with IBD extends to mental illness in the perinatal period. We found that the increased risk was mainly for postpartum women and for those diagnosed in an outpatient setting with anxiety, depression and substance use disorders. The finding of increased risk for perinatal substance use disorder requires further research to obtain a more detailed picture but is worthy of further attention given to recent increases in opioid-related deaths worldwide.[54] Since the perinatal period is a time of significant contact with the healthcare system, increased awareness by obstetricians and gastroenterologists, as well as validated tools to identify women with IBD who are at risk for, or suffering from, perinatal mental illness could prevent the onset of illness in some cases, and result in more prompt diagnosis and treatment in others. While screening tools for anxiety and depression have been developed and validated for people with IBD[55] and many addictions screening tools exist, none have thus far been validated in pregnant and postpartum women, so this may be an important next step in early identification and treatment that prevents significant morbidity for mothers and ensure health developmental trajectories for their children.

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