Histological remission in inflammatory bowel disease and risk of adverse pregnancy outcomes: A nationwide study

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Summary

Background Inflammatory bowel disease (IBD) has been linked to adverse pregnancy outcomes, but it is unclear how risks vary by histological activity.

Methods We performed a nationwide study of Swedish women diagnosed with IBD 1990–2016 and a pre-pregnancy (<12 months) colorectal biopsy with vs. without histological inflammation (1223 and 630 births, respectively). We also examined pregnancy outcomes in 2007–2016 of women with vs. without clinically active IBD (i.e., IBD-related hospitalization, surgery, or medication escalation) <12 months before pregnancy (2110 and 4993 births, respectively). Accounting for smoking, socio-demographics, and comorbidities, generalized linear models estimated adjusted risk ratios (aRRs) for preterm birth (<37 gestational weeks) and small-for-gestational age (SGA, <10th percentile weight for age).

Findings Of infants to women with vs. without histological inflammation, 9.6% (n = 117) and 6.5% (n = 41) were preterm, respectively (aRR = 1.46; 95%CI = 1.03–2.06). Histological inflammation was associated with preterm birth in ulcerative colitis (UC) (aRR = 1.64; 95%CI = 1.07–2.52), especially extensive colitis (aRR = 2.37; 95% CI = 1.12–5.02), but not in Crohn’s disease (aRR = 0.99; 95%CI = 0.55–1.78). Of infants to women with vs. without histological inflammation, 116 (9.6%) and 56 (8.9%), respectively, were SGA (aRR = 1.09; 95%CI = 0.81–1.47). Clinically active disease before pregnancy was linked to preterm birth (aRR = 1.42; 95%CI = 1.20–1.69), but not to SGA birth (aRR = 1.13; 95%CI = 0.96–1.32). Finally, of infants to women without clinical activity, histological inflammation was not significantly associated with preterm birth (aRR = 1.20; 95%CI = 0.68–2.13).

Interpretation Histological and clinical activity in IBD, especially in UC, were risk factors for preterm birth. Further research is needed to determine the importance of pre-pregnancy histological activity in women without clinically-defined disease activity.

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Keywords: Histology; Population-based; Pregnancy

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Introduction

Inflammatory bowel diseases (IBDs), represented mainly by Crohn’s disease (CD) and ulcerative colitis (UC), are chronic inflammatory conditions, impacting patients’ quality of life and imposing high societal costs. Clinical remission and mucosal healing during endoscopic evaluation are key therapeutic targets of IBD. However, microscopic disease activity can persist without clinical and endoscopic activity and has been suggested as an independent risk factor for disease flares. Histological remission (i.e., the absence of inflammation and ulceration/erosion) is therefore increasingly recognized as a potential therapeutic goal in IBD, particularly in UC.

IBD diagnosis usually coincides with childbearing years. Concerns related to adverse pregnancy outcomes are therefore common, and several studies have linked IBD to adverse pregnancy outcomes. In recent years, guidelines have underlined the importance of disease control to reduce pregnancy risks. However, these recommendations originate from data using clinical proxies for increased disease activity, such as IBD-related hospitalization, surgery, or medication, where adverse effects on pregnancy are difficult to separate from disease phenotype and patient characteristics. Despite the recent increasing appreciation of histological activity in IBD, its association with pregnancy outcomes is unknown.

Using a nationwide IBD cohort with histopathology data, we sought to investigate whether histological inflammation in IBD predicts adverse pregnancy outcomes. Our secondary aim was to determine the risk of adverse pregnancy outcomes in IBD women with and without evidence of clinical disease activity.

Methods

Study sample: Women with IBD and their infants

We defined IBD as having either ≥2 International Classification of Disease (ICD) codes in the National Patient Register (NPR) or ≥1 ICD code and ≥1 relevant colorectal histopathology code from the nationwide ESPRESSO cohort (see Supplementary Table S1). The Swedish NPR contains both inpatient and non-primary outpatient care. The ESPRESSO cohort consists of all computerized gastrointestinal histology reports from Sweden’s 28 pathology departments. This IBD definition has a 93–95% consistency with a clinical diagnosis of IBD. Moreover, we specified IBD as UC, CD, or, if a distinction between subtypes could not be made, as IBD-unclassified (IBD-U). As previously described, patients with UC and CD were characterized according to IBD-related surgery and the extent and location of the disease at diagnosis (Supplementary Tables S2 and S3). While we lacked data on the endoscopic appearance of IBD, we describe the estimated endoscopic inflammation of IBD using a validated prediction algorithm.

We identified 7374 women diagnosed with IBD in 1990–2016 who, after diagnosis, gave birth to 11,374 children in 1990–2016 (Supplementary Tables S4 and S5). 1990–2016 was chosen as a reasonable trade-off between recency (with relevance to modern IBD), and the need for a sufficient number of pregnancies to allow us to detect clinically meaningful differences.

Evidence before this study

On June 23, 2022, we searched PubMed using the following search string: (“inflammatory bowel diseases” [All Fields] OR “crohn disease” [All Fields] OR “colitis, ulcerative” [All Fields]) AND (“histology” [All Fields] OR “histological” [All Fields] OR “microscopic” [All Fields]) AND “pregnancy” [All Fields]. The search generated 21 studies; however, none of the studies concerned histological activity of inflammatory bowel disease (IBD) to pregnancy outcomes. We then searched PubMed for articles published between Jan 1, 2000, until June 23, 2022, using the following search string: (“inflammatory bowel diseases” [All Fields] OR “crohn disease” [All Fields] OR “colitis, ulcerative” [All Fields]) AND (“activity” [All Fields] OR “flare” [All Fields] OR “relapse” [All Fields]) AND “pregnancy” [All Fields]. This second search generated 250 studies, of which a large proportion were outside the scope of this study concerning aspects of IBD management and drug safety during pregnancy.

Added value of this study

Based on almost 2000 births of women with IBD with a pre-pregnancy colorectal biopsy, this nationwide study found an almost 50% increased risk of preterm birth of infants to women with histological inflammation in IBD, particularly in ulcerative colitis. Histological inflammation in IBD was not linked to other adverse pregnancy outcomes.

Implications of all available evidence

Our data support recommendations to objectively assess IBD remission status before conception, to optimise management and prevent adverse outcomes of pregnancy and IBD.
Exposures: Histological inflammation and clinical disease activity

We examined two measures of IBD activity

I. Our primary exposure was histological inflammation (vs. histological remission) documented 0–12 months (≤365 days) before the start of pregnancy. In line with recent consensus reports, histological remission was defined through ileal-colorectal histopathology (SNOMED) codes M00100/M00110 (normal mucosa), the absence of SNOMED codes for inflammation (acute or chronic), and ulceration/erosion (Supplementary Table S6). Histological inflammation was defined as ≥1 SNOMED codes for ileal-colorectal inflammation (acute or chronic) or ulceration/erosion, meaning that the histological inflammation vs. remission was defined based on the worst histological appearance across all intestinal segments. Specific scoring systems for histopathology of IBD are not routinely used in Sweden.

II. Our secondary exposure was clinically active IBD (vs. quiescent IBD). Motivated by a previous study, we defined “clinically active IBD” as IBD-related surgery, hospitalization, or at least one budesonide or corticosteroid dispensing (either systemic or locally acting), initiation of immunomodulators (e.g., thiopurines) or biologics 0–12 months before pregnancy (initiation of therapy was defined as dispensing/administration without record of such use in the previous 6 months). Data were retrieved from three high-quality national registers: the NPR, the Swedish Prescribed Drug Register, and the Swedish Quality Register for IBD (SWIBREG). Medications were identified using the Anatomical Therapeutic Chemical pharmaceutical classification system (Supplementary Table S7). Disease without these features was defined as “quiescent IBD.” The Prescribed Drug Register includes prospectively recorded data on all filled drug prescriptions since July 2005, and for this study, captured throughout 2016. To differentiate prevalent from incident therapy by using a minimum 6-month capture period of prescribed drugs, analyses of disease activity were restricted to births from October 1, 2007, throughout 2016 (e.g., a child born in 2010 to a woman diagnosed with IBD in 1992 is included in this analysis).

Adverse pregnancy outcomes

High-quality data on pregnancy outcomes were retrieved from the Medical Birth Register, which contains information on all births in Sweden since 1973. This register also records maternal age at delivery, parity, self-reported smoking (yes/no), and body mass index (BMI) at early pregnancy. Covariates were categorized as shown in Table 1 (data on smoking was missing in 4.5% and on BMI in 8.8% of pregnancies).

Our primary outcomes considered the risk of preterm birth (i.e., <37 gestational weeks; spontaneous, medically induced, and overall) and small for gestational age (SGA, <10th percentile of birth weight for gestational age and sex) birth. Gestational age was determined by second-trimester ultrasonography (since 1990, performed in some 95% of pregnant women in Sweden) or the last menstrual period as reported at the first maternity health care visit. Birth date and gestational age data were used to define the start of pregnancy.

Secondary pregnancy outcomes included very preterm birth (<32 gestational weeks), low birth weight (<2500 g), low 5-min Apgar score (<7), induction of labour, instrumental delivery, caesarean section (elective, emergency, and overall), stillbirth (data available since 2008 and classified as foetal deaths ≥22 gestational weeks), gestational diabetes and pre-eclampsia as defined in Supplementary Table S8.

Other data

As detailed in Supplementary Table S8 and Table 1, we retrieved NPR data on selected medical conditions diagnosed before delivery, which may confound the relationship between IBD and pregnancy outcomes. Socioeconomic differences strongly influence pregnancy outcomes and may be linked to IBD. Consequently, we retrieved data on the highest attained education level as a proxy for socioeconomic status. Another potential confounder was country of birth. Finally, we used NPR data to describe the proportion of births where the mother had a record of alcohol-related diseases and disorders.

Patient and public involvement

Several of the researchers of this study care for patients with IBD. However, in this register-based study no patients were directly involved in the design, recruitment or conduct of the study.

Statistical analysis

We used generalised linear models to estimate risk ratios (RRs) and their 95% confidence intervals (CIs) for adverse pregnancy outcomes of women with histological inflammation (vs. histological remission) and clinically active IBD (vs. quiescent IBD), respectively, 0–12 months before the start of pregnancy. All analyses accounted for maternal clustering due to multiple or repeated births and were further adjusted for maternal age at delivery, parity, education level, country of birth, comorbidities, early-pregnancy smoking status, and BMI.

We present complete case analyses, which ignored observations with incomplete covariate data. However,
Variable | Births in 1990-2016 | Births in Oct 2007-2016
--- | --- | ---
 | Overall | Biopsy <12 months before pregnancy | Overall | Clinical IBD activity <12 months before pregnancy
| N women with IBD | 7374 | 1164 | 611 | 5106 | 1817 | 3849
| N deliveries | 11,374 | 1223 | 630 | 7103 | 2110 | 4993
| Parity | | | | | | 
| 1 | 5073 (44.6%) | 587 (48.0%) | 299 (47.5%) | 3127 (44.0%) | 925 (43.8%) | 2202 (44.1%)
| 2 | 4440 (39.0%) | 455 (37.3%) | 244 (38.7%) | 2816 (39.6%) | 871 (41.3%) | 1945 (39.0%)
| ≥3 | 1861 (16.4%) | 180 (14.7%) | 87 (13.8%) | 1160 (16.3%) | 314 (14.9%) | 846 (16.9%)
| Smoking in early pregnancy | Yes | 725 (6.4%) | 87 (7.1%) | 39 (6.2%) | 317 (4.5%) | 116 (5.5%) | 201 (4.0%)
| No | 10,139 (89.1%) | 1085 (88.7%) | 559 (88.7%) | 6526 (91.9%) | 1917 (90.9%) | 4609 (92.3%)
| Missing data | 510 (4.5%) | 51 (4.2%) | 32 (5.1%) | 260 (3.7%) | 77 (3.6%) | 183 (3.7%)
| BMI in early pregnancy | Median (IQR) | 23.3 (21.2–26.1) | 23.5 (21.2–26.2) | 22.8 (21.0–25.2) | 23.4 (21.3–26.2) | 23.3 (21.2–26.3) | 23.4 (21.3–26.2)
| Living with partner | Yes | 10,349 (91.0%) | 1122 (91.7%) | 567 (90.0%) | 6497 (91.5%) | 1941 (92.0%) | 4571 (91.5%)
| No | 146 (1.3%) | 17 (1.4%) | 10 (1.6%) | 79 (1.1%) | 31 (1.5%) | 48 (1.0%)
| Missing data | 879 (7.7%) | 84 (6.9%) | 53 (8.4%) | 512 (7.2%) | 138 (6.5%) | 374 (7.5%)
| Level of education | ≤9 years | 770 (6.8%) | 86 (7.0%) | 54 (8.6%) | 419 (5.9%) | 150 (7.1%) | 269 (5.4%)
| 10–12 years | 4882 (42.9%) | 546 (44.6%) | 248 (39.4%) | 2651 (37.3%) | 841 (39.9%) | 1810 (36.3%)
| ≥13 years | 5685 (50.0%) | 587 (48.0%) | 327 (51.9%) | 4013 (56.5%) | 1115 (52.8%) | 2898 (58.0%)
| Missing data | 37 (0.3%) | 4 (0.3%) | 1 (0.2%) | 20 (0.3%) | 4 (0.2%) | 16 (0.3%)
| Country of birth, n (%) | Nordic | 10,534 (92.6%) | 1120 (91.6%) | 566 (89.8%) | 6497 (91.5%) | 1913 (90.7%) | 4584 (91.8%)
| Non-Nordic | 840 (7.4%) | 103 (8.4%) | 64 (10.2%) | 606 (8.5%) | 197 (9.3%) | 409 (8.2%)
| Comorbidity, n (%) | Diabetes (type 1, type 2, gestational) | 204 (1.8%) | 21 (1.7%) | 12 (1.9%) | 142 (2.0%) | 47 (2.2%) | 95 (1.9%)
| Hypertension | 106 (0.9%) | 11 (0.9%) | 4 (0.6%) | 79 (1.1%) | 24 (1.1%) | 55 (1.1%)
| Asthma | 520 (4.6%) | 50 (4.1%) | 28 (4.4%) | 424 (6.0%) | 188 (8.9%) | 236 (4.7%)
| Autoimmune disease | 846 (7.4%) | 84 (6.9%) | 52 (8.4%) | 512 (7.2%) | 138 (6.5%) | 374 (7.5%)
| Any of the above | 1525 (13.4%) | 153 (12.5%) | 87 (13.8%) | 1197 (16.9%) | 458 (21.7%) | 739 (14.8%)
| Alcohol-related disorders | 99 (0.9%) | 5 (0.4%) | 1 (0.2%) | 20 (0.3%) | 4 (0.2%) | 16 (0.3%)
| Year of IBD diagnosis, n (%) | 1990-1999 | 3427 (30.1%) | 373 (30.5%) | 143 (22.7%) | 1002 (14.1%) | 266 (12.6%) | 736 (14.7%)
| 2000-2009 | 6393 (56.2%) | 587 (48.0%) | 347 (55.1%) | 4547 (64.0%) | 1323 (62.7%) | 3224 (64.6%)
| 2010-2016 | 1554 (13.7%) | 265 (21.5%) | 140 (22.2%) | 1554 (21.9%) | 521 (24.7%) | 1031 (20.7%)
| Age (years) at IBD diagnosis | Median (IQR) | 25.2 (21.3-29.2) | 26.5 (22.1-30.4) | 25.6 (21.7-29.6) | 24.5 (20.5-28.5) | 24.2 (20.4-28.2) | 24.6 (20.5-28.6)
| Year of delivery, n (%) | 1990-1999 | 981 (8.6%) | 170 (13.9%) | 27 (4.3%) | 0 | 0 | 0
| 2000-2009 | 4746 (41.7%) | 496 (40.6%) | 229 (36.3%) | 1456 (20.5%) | 460 (21.8%) | 996 (19.9%)
| 2010-2016 | 5647 (49.6%) | 557 (45.5%) | 374 (59.4%) | 5647 (79.5%) | 1650 (78.2%) | 3997 (80.1%)
| Age (years) at delivery | Median (IQR) | 31.2 (28.0-34.5) | 30.3 (27.3-33.8) | 30.9 (27.4-34.6) | 31.5 (28.2-34.8) | 30.9 (27.5-34.4) | 31.7 (28.6-34.9)
| Time (years) from IBD diagnosis to delivery | Median (IQR) | 5 (2.4-8.8) | 2.0 (1.1-6.7) | 3.9 (1.4-9.5) | 6.3 (3.1-10.0) | 5.7 (2.6-9.5) | 6.5 (3.3-10.2)
| IBD subtype | CD | 4031 (35.4%) | 334 (27.3%) | 214 (34.0%) | 2427 (34.2%) | 841 (39.9%) | 1586 (31.8%)
| UC | 6927 (60.9%) | 831 (67.9%) | 393 (62.4%) | 4400 (61.9%) | 1171 (55.5%) | 3229 (64.7%)
| IBD-U | 416 (3.7%) | 58 (4.7%) | 23 (3.7%) | 276 (3.9%) | 98 (4.6%) | 178 (3.6%)

(Table 1 continues on next page)
### Table 1: Characteristics of births to women diagnosed with inflammatory bowel disease (IBD) in 1990–2016 giving birth in 1990–2016 (by histological inflammation) and in October 2007–2016 (by proxies for clinical IBD activity).

| Variable | Births in 1990-2016 | Births in Oct 2007–2016 |
|----------|----------------------|-------------------------|
|          | Overall | Biopsy <12 months before pregnancy<sup>a</sup> | Overall | Clinical IBD activity <12 months before pregnancy<sup>b</sup> |
|          |         | Histological inflammation | Histological remission | Clinically active | Clinically quiescent |
|         |         |                                      |                        |                           |                           |
| Montreal classification CD<sup>d</sup> |         |                                      |                        |                           |                           |
| L1/L2/LX | 3018 (74.9%) | 231 (69.2%) | 164 (76.6%) | 1995 (82.2%) | 695 (82.6%) | 1300 (82.0%) |
| L2      | 612 (15.2%) | 58 (17.4%) | 40 (18.7%) | 387 (15.9%) | 141 (16.8%) | 246 (15.5%) |
| L missing/ICD code before 1997 | 401 (9.9%) | 45 (13.5%) | 10 (4.7%) | 45 (1.9%) | 5 (0.6%) | 40 (2.5%) |
|         |         |                                      |                        |                           |                           |
| Montreal classification UC<sup>d</sup> |         |                                      |                        |                           |                           |
| E1/E2   | 2660 (38.4%) | 297 (35.7%) | 152 (38.4%) | 1901 (43.2%) | 362 (30.9%) | 1539 (47.7%) |
| E3      | 2290 (33.1%) | 315 (37.9%) | 147 (37.4%) | 1691 (38.4%) | 605 (51.7%) | 1086 (32.6%) |
| EX      | 1380 (19.9%) | 136 (16.4%) | 78 (19.8%) | 762 (17.3%) | 193 (16.5%) | 569 (17.6%) |
| E missing/ICD code before 1997 | 597 (8.6%) | 83 (10.0%) | 16 (4.1%) | 46 (1.0%) | 11 (0.9%) | 35 (1.1%) |
|         |         |                                      |                        |                           |                           |
| Endoscopy<sup>e</sup> |         |                                      |                        |                           |                           |
| Ever before pregnancy | 10,637 (93.5%) | 1223 (100%) | 630 (100%) | 6777 (95.4%) | 2077 (98.4%) | 4700 (94.1%) |
| 0–<12 months | 3330 (29.3%) | 1223 (100%) | 630 (100%) | 2065 (29.1%) | 1050 (49.8%) | 1015 (20.3%) |
| 0–<6 months | 1944 (17.1%) | 740 (60.5%) | 378 (60.0%) | 1197 (16.9%) | 651 (30.9%) | 546 (10.9%) |
| During pregnancy | 1614 (14.2%) | 249 (20.4%) | 88 (14.1%) | 1005 (14.1%) | 350 (16.6%) | 655 (13.1%) |
|         |         |                                      |                        |                           |                           |
| Endoscopic inflammation <12m before pregnancy (Ref. 17) |         |                                      |                        |                           |                           |
| Low inflammation | 493 (4.3%) | 43 (3.5%) | 432 (68.6%) | 328 (4.6%) | 129 (6.1%) | 199 (4.0%) |
| High inflammation | 1988 (17.5%) | 1180 (96.5%) | 198 (31.4%) | 1142 (16.1%) | 350 (16.6%) | 655 (13.1%) |
|         |         |                                      |                        |                           |                           |
| Clinically active IBD<sup>d</sup> |         |                                      |                        |                           |                           |
| Births from October 2007 until 2016 | 7103 (62.4%) | 691 (56.5%) | 436 (69.2%) | 7103 (100%) | 2110 (100%) | 4993 (100%) |
| IBD-related hospitalization | 1346 (11.8%) | 337 (27.6%) | 110 (17.5%) | 748 (10.5%) | 748 (35.5%) | 0 |
| IBD-related surgery | 295 (2.6%) | 90 (7.4%) | 23 (3.7%) | 147 (2.1%) | 147 (7.0%) | 0 |
| IBD-related drugs | 2018 (28.4%) | 666 (53.0%) | 167 (40.4%) | 1808 (25.5%) | 1808 (85.7%) | 0 |
| Corticosteroid | 1457 (21.1%) | 293 (42.4%) | 134 (30.7%) | 1370 (19.4%) | 1370 (64.9%) | 0 |
| Budesonide | 395 (5.6%) | 67 (9.7%) | 59 (13.5%) | 351 (4.9%) | 351 (16.6%) | 0 |
| Immunomodulators | 556 (7.8%) | 101 (14.6%) | 41 (9.4%) | 469 (6.6%) | 469 (22.2%) | 0 |
| Biologics | 162 (2.3%) | 35 (5.1%) | 14 (3.2%) | 148 (2.1%) | 148 (7.0%) | 0 |
|         |         |                                      |                        |                           |                           |
| Time (months) from biopsy to start of pregnancy |         |                                      |                        |                           |                           |
| Mean (SD) | 5.7 (3.4) | 5.6 (3.4) | 0 | 5.7 (3.4) | 5.6 (3.4) | 0 |
| Median (IQR) | 5.7 (2.7–8.5) | 5.7 (2.7–8.5) | 0 | 5.7 (2.7–8.5) | 5.7 (2.7–8.5) | 0 |
|         |         |                                      |                        |                           |                           |
| Biopsy 0–<12 months before pregnancy |         |                                      |                        |                           |                           |
| Births from October 2007 until 2016 | 1853 (16.3%) | 1223 (100%) | 0 | 1127 (15.9%) | 547 (25.9%) | 580 (11.3%) |
| Inflammation | 1223 (66.0%) | 1223 (100%) | 0 | 691 (61.3%) | 373 (68.2%) | 318 (54.8%) |
| Remission | 630 (34.0%) | 630 (100%) | 0 | 436 (38.7%) | 174 (31.8%) | 262 (45.2%) |

BMI, body mass index (kg/m<sup>2</sup>); CD, Crohn’s disease; IBD-U, IBD-unclassified; IQR, interquartile range; SD, standard deviation; UC, ulcerative colitis. <sup>a</sup>Histopathology reports, as recorded in the ESPRESSO cohort, originating from the ileum or colorectum (topographic codes T65, T67, and T68) with SNOMED code for inflammation and normal histology, respectively, as detailed in Supplementary Table S6. 
<sup>b</sup>Clinical IBD activity defined as IBD-related surgery, hospitalization, or IBD medication as detailed in Supplementary Table S7. Definitions of comorbidities are listed in Supplementary Table S8. 
<sup>d</sup>Extent and location of disease at the time of diagnosis as detailed in Supplementary Table S2. 
<sup>e</sup>Upper or lower endoscopy as recorded in the National Patient Register (NPR), The Swedish Quality Register for IBD or ESPRESSO histology data.
in sensitivity analyses for the outcomes preterm birth and SGA we used multiple imputation to account for missing BMI and smoking data.

Our primary outcomes of preterm birth and SGA were examined by IBD subtype (UC, CD, IBD-U) and the extent and location of disease at diagnosis. The risks of preterm birth and SGA were also analysed stratified by year of IBD diagnosis (1990–1999, 2000–2009, 2010–2016), duration of IBD diagnosis at delivery (<2, ≥2 years), age at delivery (15–24, 25–29, 30–34, 35–39, 40–44 years), parity (nulliparous, parous), maternal education level (≤9, 10–12, ≥13 years of education), and country of birth (Nordic, Other).

**We performed the following sensitivity analyses**

**Exposure window** restricted to 0–<6 months before or during pregnancy (i.e., start of pregnancy until birth).

**Histological inflammation in women without clinically active IBD.** We determined the possible incremental effect of residual histological inflammation in women without clinical disease activity. Restricting data to births from October 1, 2007, through 2016, we estimated the risk of preterm birth and SGA in women with histological inflammation, but without clinical disease activity (i.e., “clinical activity = 0” and “inflammation = 0” [reference category] vs. “clinical activity = 0” but “inflammation = 1”).

**Outcome definition.** To test the robustness of our findings, SGA was also defined as below –2 standard deviations of weight for age and sex.

**Post-hoc analysis**

Stratified analyses of histological inflammation and preterm birth by use of corticosteroids: Restricted to births between October 2007 and December 2016 for which Prescribed Drug Registry data were available, we stratified our analysis on histological inflammation (vs histological remission) and preterm birth by pre-pregnancy use of corticosteroids.

Data were analysed using SAS version 9.4 (SAS Institute, Inc).

The Stockholm Ethics Review Board approved the study and waived the requirement of informed consent.

**Role of the funding source**

The funding sources did not influence any aspect of the study (its design, the collection, analysis, and interpretation of data), its writing or the decision to submit it for publication. JFL, JS and OO had full access to all the data in the study. All authors accepted responsibility to submit the paper for publication.

**Results**

**Patient characteristics: Histological inflammation vs. histological remission**

This study included 7374 women diagnosed with IBD between 1990 and 2016 who, after their diagnosis, gave birth to 11,374 children (up until 2016). Restricting our sample to women with ileal-colorectal biopsies collected 0–<12 months before pregnancy, there were 1223 births to 1164 women with histological inflammation and 630 births to 611 women with histological remission (Table 1). Median 2 (range 1–13) biopsies from colorectum and terminal ileum were obtained in each patient.

Overall, 35.4% of the children were born by women with CD, 60.9% with UC, and 3.7% with IBD-U. Women with histological inflammation more often had a high degree of endoscopic inflammation and a higher risk of IBD-related surgery or hospitalization in the year before pregnancy than those in histological remission (Table 1). Until delivery, the median disease duration was shorter in the inflammation group (2.0 years) than those without histological inflammation (3.9 years). Pre-pregnancy histological inflammation was more common in births in the 1990s than after 2000 (Table 1). However, smoking habits, BMI, parental cohabitation, and education level were similar in women with and without histological inflammation (Table 1).

**Main results: Histological inflammation of IBD and risk of preterm birth and SGA**

The preterm birth rate was 7.8% (n = 887/11,322) in the overall sample of IBD women. Among those with histologic inflammation within 12 months before pregnancy, 9.6% (n = 117) of births were preterm compared to 6.5% (n = 41) in women with no inflammation corresponding to an almost 50% increased risk of preterm birth (RR 1.46; 95%CI 1.04–2.05) and represents one extra event per 32 births in women with histological inflammation. Adjustment for maternal age, smoking habits, BMI, parental cohabitation, and comorbidity exerted negligible impact on results (adjusted (a)RR 1.46 (95% CI 1.03–2.06; Table 2). Risks were numerically higher for medically induced (aRR 1.88; 95%CI 0.96–3.67) than spontaneous preterm births (aRR 1.31; 95%CI 0.86–1.98). In sensitivity analyses the aRRs for preterm birth were similar for histological inflammation within 6 months before pregnancy (aRR 1.41; 95%CI 0.90–2.21) and histological inflammation during pregnancy (aRR 1.38; 95%CI 0.72–2.64).

Excess risks of preterm birth were confined to women with histological inflammation in UC (aRR 1.64; 95%CI 1.07–2.52), and especially elevated in those with extensive colitis (Montreal classification E3 of UC, aRR 2.37; 95%CI 1.12–5.02). In contrast, histological...
| Group | Live births in all women | Live births in women with histological inflammation | Risk ratio (95% CI) | Adjusted risk ratio (95% CI) |
|-------|------------------------|---------------------------------------------|------------------|--------------------------|
| N live births | 11,322 | 1218 | 627 | |
| Overall, any preterm birth | 887 (7.8%) | 117 (9.6%) | 41 (6.5%) | 1.46 (1.04–2.06) | 1.46 (1.03–2.06) |
| Medically induced | 328 (2.9%) | 41 (3.4%) | 11 (1.8%) | 1.93 (0.99–3.75) | 1.88 (0.96–3.67) |
| Spontaneous | 559 (4.9%) | 76 (6.2%) | 30 (4.8%) | 1.31 (0.86–1.97) | 1.31 (0.86–1.98) |

### Stratified analyses

| IBD subtype | Live births | Histological inflammation | Risk ratio (95% CI) | Adjusted risk ratio (95% CI) |
|-------------|-------------|--------------------------|------------------|--------------------------|
| CD | 301 (7.5%) | 23 (6.9%) | 16 (7.5%) | 0.92 (0.51–1.68) | 0.99 (0.55–1.78) |
| UC | 550 (8.0%) | 88 (16.6%) | 24 (6.1%) | 1.70 (1.11–2.60) | 1.64 (1.07–2.52) |
| IBD-U | 36 (8.7%) | 6 (10.3%) | 1 (4.3%) | 2.31 (0.31–17.49) | - |

| Montreal classification CD | Live births | Histological inflammation | Risk ratio (95% CI) | Adjusted risk ratio (95% CI) |
|---------------------------|-------------|--------------------------|------------------|--------------------------|
| L1/L3/LX | 240 (8.0%) | 18 (7.8%) | 14 (8.6%) | 0.92 (0.47–1.79) | 1.15 (0.58–2.28) |
| L2 | 38 (6.2%) | 3 (5.2%) | 1 (2.5%) | - | - |

| Montreal classification UC | Live births | Histological inflammation | Risk ratio (95% CI) | Adjusted risk ratio (95% CI) |
|---------------------------|-------------|--------------------------|------------------|--------------------------|
| E1/E2 | 160 (6.0%) | 17 (5.7%) | 9 (5.9%) | 0.97 (0.44–2.12) | - |
| E3 | 221 (9.7%) | 40 (18.2%) | 8 (5.5%) | 2.28 (1.12–4.66) | 2.37 (1.12–5.02) |
| EX | 114 (8.3%) | 16 (11.8%) | 5 (6.4%) | 1.83 (0.70–4.80) | 1.66 (0.63–4.37) |

### Year of IBD diagnosis, n (%)

| Year of IBD diagnosis, n (%) | Live births | Histological inflammation | Risk ratio (95% CI) | Adjusted risk ratio (95% CI) |
|-----------------------------|-------------|--------------------------|------------------|--------------------------|
| 1990–1999 | 286 (8.4%) | 40 (10.8%) | 13 (9.1%) | 1.19 (0.65–2.17) | 1.13 (0.62–2.04) |
| 2000–2009 | 476 (7.5%) | 55 (9.4%) | 20 (5.8%) | 1.61 (0.99–2.62) | 1.57 (0.96–2.57) |
| 2010–2016 | 125 (8.1%) | 22 (8.4%) | 8 (5.8%) | 1.48 (0.67–2.41) | - |

| Time (years) from IBD diagnosis to delivery | Live births | Histological inflammation | Risk ratio (95% CI) | Adjusted risk ratio (95% CI) |
|-------------------------------------------|-------------|--------------------------|------------------|--------------------------|
| ≤2 years | 225 (9.3%) | 58 (9.5%) | 13 (5.8%) | 1.68 (0.93–3.01) | 1.63 (0.92–2.88) |
| ≥2 years | 662 (7.4%) | 59 (9.7%) | 28 (7.0%) | 1.39 (0.90–2.13) | 1.35 (0.87–2.11) |

| Age at delivery | Live births | Histological inflammation | Risk ratio (95% CI) | Adjusted risk ratio (95% CI) |
|-----------------|-------------|--------------------------|------------------|--------------------------|
| 15-24 years | 305 (9.8%) | 12 (8.1%) | 4 (7.3%) | 1.38 (0.41–4.71) | - |
| 25-29 years | 286 (8.1%) | 41 (9.5%) | 14 (6.6%) | 1.44 (0.80–2.58) | 1.47 (0.83–2.62) |
| 30-34 years | 301 (7.1%) | 35 (8.8%) | 16 (7.3%) | 1.21 (0.69–2.13) | 1.80 (0.83–3.91) |
| 35-39 years | 161 (7.8%) | 24 (11.7%) | 7 (7.5%) | 1.93 (0.86–4.35) | 1.91 (0.84–4.33) |
| 40-44 years | 34 (8.5%) | 5 (14.3%) | 0 | - | - |

| Parity | Live births | Histological inflammation | Risk ratio (95% CI) | Adjusted risk ratio (95% CI) |
|--------|-------------|--------------------------|------------------|--------------------------|
| Nulliparous | 488 (9.7%) | 58 (9.9%) | 22 (7.4%) | 1.35 (0.84–2.16) | 1.41 (0.88–2.26) |
| Parous | 399 (6.4%) | 59 (9.3%) | 19 (5.8%) | 1.61 (0.98–2.66) | 1.63 (0.99–2.69) |

| Level of education | Live births | Histological inflammation | Risk ratio (95% CI) | Adjusted risk ratio (95% CI) |
|-------------------|-------------|--------------------------|------------------|--------------------------|
| ≤9 years | 67 (8.8%) | 10 (11.8%) | 4 (7.4%) | 1.58 (0.52–4.78) | 1.70 (0.45–6.45) |
| 10-12 years | 402 (8.3%) | 52 (6.6%) | 14 (5.7%) | 1.67 (0.95–2.95) | 1.64 (0.93–2.96) |
| ≥13 years | 415 (7.3%) | 55 (9.4%) | 27 (7.0%) | 1.31 (0.83–2.07) | 1.35 (0.85–2.13) |

| Country of birth, n (%) | Live births | Histological inflammation | Risk ratio (95% CI) | Adjusted risk ratio (95% CI) |
|------------------------|-------------|--------------------------|------------------|--------------------------|
| Nordic | 816 (7.8%) | 104 (12.9%) | 35 (6.2%) | 1.49 (1.03–2.16) | 1.50 (1.03–2.16) |
| Non-Nordic | 71 (8.5%) | 13 (18.7%) | 6 (9.4%) | 1.38 (0.54–3.40) | - |

### Sensitivity analyses

| Modified exposure window | Live births | Histological inflammation | Risk ratio (95% CI) | Adjusted risk ratio (95% CI) |
|--------------------------|-------------|--------------------------|------------------|--------------------------|
| 0–6 months before pregnancy | 63 (9.7%) | 24 (7.0%) | 1.38 (0.88–2.16) | 1.41 (0.90–2.21) |
| During pregnancy | 49 (13.0%) | 9 (9.3%) | 1.34 (0.72–2.48) | 1.38 (0.72–2.64) |

CI, confidence interval; CD, Crohn’s disease; IBD-U, IBD-unclassified; UC, ulcerative colitis. Histological inflammation was defined as having an ideal-colorectal histology report with ≥1 histopathology (SNOMED) codes for inflammation (Supplementary Table S6). Histological remission was defined through SNOMED codes M00100/M00110 (normal mucosa) and no presence of SNOMED codes for inflammation. Clustered on the identity of the woman. Clustered on the identity of the woman and adjusted for maternal age at delivery, parity, smoking in early pregnancy, body mass index (BMI) in early pregnancy, education, and comorbidity (any diabetes, hypertension, chronic autoimmune disease, and asthma; Supplementary Table S8). The model failed to converge in specific analyses (denoted by “-”). Causes for medically induced preterm birth include, among others, antepartum haemorrhage and pre-eclampsia. Extent and location of disease at diagnosis as detailed in Supplementary Table S2.

Table 2: Risk of any preterm birth according to histological inflammation of inflammatory bowel disease (IBD) < 12 months before pregnancy.
inflammation in CD was not associated with preterm birth (aRR 0.99; 95%CI 0.55–1.78). While the absolute risks of preterm birth were highest in nulliparous women, young women (15–24 years), and those with low education level (<9 years) (Table 2), the RRs by histological activity were otherwise relatively consistent across subgroups of patient characteristics (Table 2).

Women with pre-pregnancy histological inflammation gave birth to 116 (9.6%) SGA infants and those without to 56 (8.9%) (aRR 1.09; 95%CI 0.81–1.47) (overall, SGA was observed in 9.6% [n = 1083/11,322] of infants to women with IBD). Neither inflammation 0–6 months before pregnancy (aRR 0.83; 95%CI 0.54–1.25) nor inflammation during pregnancy (aRR 1.21; 95%CI 0.58–2.52) was significantly associated with SGA (Table 3). Histological inflammation was also not significantly associated with SGA within patient subgroups (Table 3).

**Patient characteristics: Clinically active IBD vs. quiescent IBD**

From October 1, 2007, and until 2016, approximately one third (n = 2110) of the study infants were born to women with clinically active IBD and two thirds (n = 4993) were born to women with clinically quiescent IBD. Almost 90% of those with clinically active IBD were identified through their use of IBD-related drugs (Table 1). Characteristics of women with active IBD were similar to women with histological inflammation (Table 1). Two thirds (68.2%; n = 373/547) and 54.8% (n = 318/580) of women with and without clinically active IBD, respectively, had histological inflammation within 12 months before pregnancy (Table 1).

**Clinically active IBD and risk of preterm birth and SGA**

In women with clinically active IBD 0–12 months before pregnancy, 9.8% (n = 206) of births were preterm compared to 6.5% (n = 325) of births to women with clinically quiescent IBD (aRR 1.42; 95%CI 1.20–1.69). There was a higher risk of preterm birth in women with clinical IBD activity during pregnancy (aRR 1.71; 95%CI 1.45–2.02; Table 4). In line with the results for histological inflammation, the highest aRRs for preterm birth were observed in women with active extensive UC (Montreal classification E3 [pancolitis], aRR 1.84 [95%CI 1.37–2.48]; Montreal E1/E2 [proctitis/left-sided UC], aRR 1.09 [95%CI 0.69–1.74]). Clinically active IBD was associated with both medically induced preterm birth (aRR 1.49; 95%CI 1.12–1.99) and spontaneous preterm birth (aRR 1.41; 95%CI 1.13–1.76) (Table 4).

Some 203 (9.7%) and 416 (8.4%) infants born to women with and without clinically active IBD <12 months before pregnancy, respectively, were SGA (aRR = 1.13; 95%CI 0.96–1.32). Active IBD before pregnancy was also not significantly associated with SGA within patient subgroups of varying education levels, ages, etc (Supplementary Table S9). However, there was a modestly increased SGA risk in children to women with active IBD during pregnancy (aRR 1.17 [95% CI 1.01–1.37]; Supplementary Table S9).

**Preterm birth and SGA related to histological inflammation in clinically quiescent IBD**

In a sensitivity analysis of 726 children to women with clinically quiescent IBD, the presence of histological inflammation (vs. no inflammation) was not significantly associated with preterm birth (aRR 1.20; 95%CI 0.68–2.13; Table 5) (for reference, the main analysis for inflammation yielded an aRR of 1.46 [95%CI 1.03–2.06]). Histological inflammation in clinically quiescent IBD was not associated with SGA (aRR 0.98; 95%CI 0.60–1.60).

**Secondary pregnancy outcomes**

For our secondary outcomes, caesarean section was more prevalent in women with (31.8%) vs. without (24.3%) clinically active IBD (aRR 1.25; 95%CI 1.17–1.34; Supplementary Table S10). However, caesarean section was not significantly linked to histologic inflammation (25.8% [inflammation] vs. 23.0% [remission]; aRR 1.10; 95%CI 0.93–1.30; Supplementary Table S11). Pre-eclampsia was not linked to histologic inflammation or clinical IBD activity (Supplementary Tables S10 and S11).

**Post-hoc analysis**

Restricting our cohort to children born between October 2007 and December 2016 (period for which maternal data on drugs were available) we reran our analysis on histological inflammation and preterm birth while stratifying for corticosteroid use. However, these analyses yielded largely similar estimates across strata (in women with corticosteroid use: aHR = 1.30; 95% CI 0.66–2.55; in women without corticosteroid use: aHR = 1.35; 95% CI 0.77–2.36).

The association of histological inflammation vs histological remission and clinically active vs quiescent IBD with SGA and preterm birth were largely unchanged when adjusting for alcohol-related diseases and disorders (Supplementary Table S12) as well as when using multiple imputation to account for missing BMI and smoking covariate data (Supplementary Tables S13 and S14).

**Discussion**

In this nationwide study of maternal IBD, histological inflammation was associated with preterm birth, but not other adverse pregnancy outcomes. The increased risk
| Group | Live births in all women | Live births in women with histological inflammation | Risk ratio (95% CI) Adjusted risk ratio (95% CI) |
|-------|--------------------------|-----------------------------------------------|---------------------------------------------|
|       | 11,322                   | 1218                                          | 627                                         |
| N live births | Overall, SGA (<10 percentile) | 1083 (9.6%) | 116 (9.6%) | 56 (8.9%) | 1.06 (0.78–1.43) | 1.09 (0.81–1.47) |
|       | SGA < –2SD               | 323 (2.9%)                                   | 36 (3.0%)                                   | 16 (2.6%)                                   | 1.16 (0.65–2.07) | – |
| Stratified analyses | IBD subtype |                      |                                              |                                             |
|       | CD                       | 404 (10.1%)                                   | 25 (10.5%)                                   | 22 (10.4%)                                   | 1.01 (0.64–1.60) | 0.96 (0.60–1.54) |
|       | UC                       | 629 (9.3%)                                    | 77 (9.3%)                                    | 31 (7.9%)                                    | 1.17 (0.79–1.74) | 1.18 (0.80–1.74) |
|       | IBD-U                    | 40 (9.7%)                                     | 4 (6.9%)                                     | 3 (13.0%)                                    | 0.57 (0.14–2.42) | – |
| Montre | Montreal classification CD |                       |                                              |                                             |
|       | L1/L3/LX                 | 293 (9.8%)                                    | 22 (6.9%)                                    | 16 (9.9%)                                    | 0.97 (0.53–1.79) | 1.06 (0.57–1.95) |
|       | L2                       | 65 (10.6%)                                    | 6 (10.3%)                                    | 5 (12.5%)                                    | 1.00 (0.99–1.00) | – |
| Montre | Montreal classification UC |                      |                                              |                                             |
|       | E1/E2                    | 228 (8.6%)                                    | 21 (7.1%)                                    | 15 (9.9%)                                    | 0.72 (0.38–1.36) | 0.67 (0.35–1.27) |
|       | E3                       | 201 (8.9%)                                    | 29 (9.2%)                                    | 13 (9.0%)                                    | 1.04 (0.56–1.93) | 1.39 (0.76–2.56) |
|       | EX                       | 134 (9.8%)                                    | 13 (9.6%)                                    | 2 (2.6%)                                     | 3.69 (0.87–15.68) | – |
| Year of IBD diagnosis, n (%) |                      |                                              |                                             |                                             |
|       | 1990–1999                | 386 (11.4%)                                   | 46 (12.5%)                                   | 14 (9.8%)                                    | 1.20 (0.72–1.99) | 1.20 (0.71–2.04) |
|       | 2000–2009                | 562 (8.8%)                                    | 52 (8.9%)                                    | 34 (9.9%)                                    | 0.90 (0.60–1.36) | 1.02 (0.69–1.53) |
|       | 2010–2016                | 135 (8.7%)                                    | 18 (6.9%)                                    | 8 (5.8%)                                     | 1.19 (0.52–2.68) | 1.10 (0.47–2.58) |
| Time (years) from IBD diagnosis to delivery |                      |                                              |                                             |                                             |
|       | <2 years                 | 238 (9.9%)                                    | 57 (9.4%)                                    | 12 (5.3%)                                    | 1.77 (0.97–3.23) | 1.70 (0.91–3.18) |
|       | ≥2 years                 | 845 (9.5%)                                    | 59 (9.7%)                                    | 44 (11.0%)                                   | 0.89 (0.62–1.27) | 0.94 (0.66–1.34) |
| Age at delivery |                      |                                              |                                             |                                             |
|       | 15–24 years              | 138 (13.0%)                                   | 17 (11.5%)                                   | 5 (9.1%)                                     | 3.66 (1.15–11.64) | 1.33 (0.50–3.57) |
|       | 25–29 years              | 348 (9.9%)                                    | 46 (10.7%)                                   | 19 (9.0%)                                    | 1.19 (0.72–1.97) | 1.14 (0.79–1.87) |
|       | 30–34 years              | 370 (8.7%)                                    | 32 (8.1%)                                    | 19 (8.7%)                                    | 0.93 (0.54–1.60) | 0.99 (0.58–1.69) |
|       | 35–39 years              | 185 (9.0%)                                    | 20 (8.8%)                                    | 9 (7.8%)                                     | 1.00 (1.00–1.00) | – |
|       | 40–44 years              | 42 (10.5%)                                    | 1 (2.9%)                                     | 4 (16.0%)                                    | 0.18 (0.02–1.50) | – |
| Parity | Nulliparous              | 692 (13.7%)                                   | 72 (12.4%)                                   | 34 (11.4%)                                   | 1.08 (0.74–1.59) | 1.17 (0.80–1.71) |
|       | Parous                   | 391 (6.2%)                                    | 44 (7.0%)                                    | 22 (6.7%)                                    | 1.01 (0.63–1.64) | 0.87 (0.53–1.44) |
| Level of education |          |                                              |                                             |                                             |
|       | ≤59 years                | 118 (15.5%)                                   | 10 (11.8%)                                   | 10 (18.5%)                                   | 0.63 (0.34–1.18) | – |
|       | 10–12 years              | 494 (10.2%)                                   | 56 (10.4%)                                   | 25 (10.2%)                                   | 1.01 (0.65–1.56) | 1.01 (0.65–1.56) |
|       | ≥13 years                | 465 (8.2%)                                    | 50 (8.5%)                                    | 21 (6.4%)                                    | 1.32 (0.81–2.15) | 1.41 (0.86–2.30) |
| Country of birth, n (%) |                      |                                              |                                             |                                             |
|       | Nordic                   | 971 (9.3%)                                    | 107 (9.6%)                                   | 47 (8.4%)                                    | 1.14 (0.83–1.57) | 1.17 (0.86–1.61) |
|       | Non-Nordic               | 112 (13.4%)                                   | 9 (8.8%)                                     | 9 (14.1%)                                    | 0.63 (0.26–1.49) | 0.61 (0.22–1.67) |

Sensitivity analyses

Modified exposure window

|          | 0–6 months before pregnancy |                                            |                                               |
|----------|-----------------------------|---------------------------------------------|---------------------------------------------|
|          | 11,322                      | 1218                                        | 627                                         |
|          | 52 (8.0%)                   | 33 (9.6%)                                   | 0.83 (0.55–1.26)                            | 0.83 (0.54–1.25) |
|          | 41 (10.9%)                  | 8 (8.2%)                                    | 1.32 (0.64–2.73)                            | 1.21 (0.58–2.52) |

CI, confidence interval; CD, Crohn’s disease; IBD-U, IBD-unclassified; SD, standard deviation; UC, ulcerative colitis. SGA defined as birthweights <10th percentile (or < –2SD) for gestational age and sex of all singleton births in 1983–2010 in Sweden. Histological inflammation was defined as having an ileal-colonrectal histology report with ≥2 histopathology (SNOMED) codes for inflammation (Supplementary Table S5). Histological remission was defined through SNOMED codes M00100/M00110 (normal mucosa) and no presence of SNOMED codes for inflammation. Clustered on the identity of the woman. Clustered on the identity of the woman and adjusted for maternal age at delivery, parity, smoking in early pregnancy, body mass index (BMI) in early pregnancy, education, and comorbidity (any diabetes, hypertension, chronic autoimmune disease, and asthma; Supplementary Table S8). The model failed to converge in specific analyses (denoted by “–”). Missing data for birth weight, all women with IBD n = 24 (0.2%), histological inflammation n = 4 (0.3%) and histological remission n = 1 (0.2%). Extent and location of disease at diagnosis as detailed in Supplementary Table S2.

Table 3: Risk of small for gestational age (SGA, <10th percentile of birth weight by age) according to histological inflammation of inflammatory bowel disease (IBD) < 12 months before pregnancy.
### Table 4: Risk of any preterm birth according to clinically active inflammatory bowel disease (IBD) ≤12 months before pregnancy

| Group                                      | Live births in all women | Live births in women with clinically active IBD | Live births in women with clinically quiescent IBD | Risk ratio† (95% CI) | Adjusted risk ratio† (95% CI) |
|--------------------------------------------|--------------------------|-----------------------------------------------|-----------------------------------------------|----------------------|--------------------------------|
| **N live births**                          | 2064                     | 2094                                          | 4870                                          |                      |                                |
| Overall, any preterm birth                 |                          |                                               |                                               | 1.45 (1.23-1.72)     | 1.42 (1.20-1.69)             |
| Medically induced                          | 531 (7.5%)               | 206 (9.8%)                                    | 325 (6.5%)                                    |                      |                                |
| Spontaneous                                | 203 (7.9%)               | 81 (3.9%)                                     | 122 (2.5%)                                    | 1.53 (1.15-2.03)     | 1.49 (1.12-1.99)             |
| Stratiﬁed analyses                         |                          |                                               |                                               | 1.44 (1.15-1.79)     | 1.41 (1.13-1.76)             |
| IBD subtype                                |                          |                                               |                                               |                      |                                |
| CD                                         | 173 (7.2%)               | 70 (8.4%)                                     | 103 (6.5%)                                    | 1.28 (0.95-1.73)     | 1.22 (0.90-1.66)             |
| UC                                         | 335 (7.7%)               | 128 (11.0%)                                   | 207 (6.4%)                                    | 1.64 (1.33-2.04)     | 1.62 (1.31-2.01)             |
| IBD-U                                      | 23 (8.4%)                | 8 (8.2%)                                      | 15 (8.5%)                                     | 1.00 (0.44-2.24)     | 0.98 (0.48-2.22)             |
| Montreal classiﬁcation CD†                 |                          |                                               |                                               |                      |                                |
| L1/L3/LX                                   | 148 (7.5%)               | 61 (8.8%)                                     | 87 (6.7%)                                     | 1.29 (0.93-1.80)     | 1.22 (0.87-1.72)             |
| L2                                         | 22 (5.7%)                | 9 (6.4%)                                      | 13 (5.3%)                                     | 1.21 (0.53-2.76)     | 1.33 (0.66-2.71)             |
| Montreal classiﬁcation UC†                 |                          |                                               |                                               |                      |                                |
| E1/E2                                      | 108 (5.7%)               | 23 (6.4%)                                     | 85 (5.5%)                                     | 1.12 (0.71-1.77)     | 1.09 (0.69-1.74)             |
| E3                                         | 159 (9.5%)               | 82 (13.7%)                                    | 77 (7.2%)                                     | 1.84 (1.37-2.48)     | 1.84 (1.37-2.48)             |
| EX                                         | 65 (8.6%)                | 22 (11.5%)                                    | 43 (7.6%)                                     | 1.52 (0.93-2.48)     | 1.44 (0.87-2.39)             |
| Year of IBD diagnosis, n (%)               |                          |                                               |                                               |                      |                                |
| 1990–1999                                  | 72 (7.3%)                | 25 (9.5%)                                     | 48 (6.6%)                                     | 1.42 (0.88-2.28)     | 1.41 (0.89-2.33)             |
| 2000–2009                                  | 333 (7.4%)               | 120 (9.0%)                                    | 213 (6.3%)                                    | 1.51 (1.22-1.88)     | 1.47 (1.18-1.82)             |
| 2010–2016                                  | 125 (8.1%)               | 51 (9.8%)                                     | 74 (7.2%)                                     | 1.32 (0.94-1.86)     | 1.35 (0.96-1.90)             |
| Time (years) from IBD diagnosis to delivery|                          |                                               |                                               |                      |                                |
| <2 years                                   | 102 (9.0%)               | 40 (9.8%)                                     | 62 (8.6%)                                     | 1.13 (0.77-1.66)     | 1.14 (0.77-1.69)             |
| ≥2 years                                   | 429 (7.2%)               | 166 (9.8%)                                    | 263 (6.2%)                                    | 1.53 (1.27-1.86)     | 1.49 (1.23-1.81)             |
| Age at delivery                            |                          |                                               |                                               |                      |                                |
| 15–24 years                                | 61 (9.9%)                | 28 (11.8%)                                    | 33 (8.8%)                                     | 1.23 (0.75-2.00)     | 1.17 (0.71-1.92)             |
| 25–29 years                                | 155 (7.4%)               | 58 (8.6%)                                     | 97 (6.9%)                                     | 1.23 (0.91-1.67)     | 1.18 (0.87-1.60)             |
| 30–34 years                                | 179 (6.6%)               | 71 (9.7%)                                     | 108 (5.5%)                                    | 1.76 (1.31-2.36)     | 1.75 (1.30-2.36)             |
| 35–39 years                                | 112 (8.1%)               | 40 (11.0%)                                    | 72 (7.0%)                                     | 1.53 (1.05-2.23)     | 1.46 (1.00-2.14)             |
| 40–44 years                                | 24 (8.6%)                | 9 (10.8%)                                     | 15 (7.7%)                                     | 1.30 (0.68-2.58)     | -                              |
| Parity                                     |                          |                                               |                                               |                      |                                |
| Nulliparous                                | 284 (9.1%)               | 104 (11.3%)                                   | 180 (8.2%)                                    | 1.38 (1.10-1.73)     | 1.36 (1.08-1.72)             |
| Parous                                     | 247 (6.2%)               | 102 (8.7%)                                    | 145 (5.2%)                                    | 1.65 (1.29-2.11)     | 1.55 (1.21-2.00)             |
| Level of education                         |                          |                                               |                                               |                      |                                |
| ≤9 years                                   | 32 (7.8%)                | 13 (8.8%)                                     | 19 (7.2%)                                     | 1.24 (0.63-2.44)     | 1.16 (0.59-2.31)             |
| 10–12 years                                | 217 (8.2%)               | 89 (10.6%)                                    | 128 (7.1%)                                    | 1.44 (1.10-1.87)     | 1.44 (1.11-1.87)             |
| ≥13 years                                  | 279 (7.0%)               | 104 (9.4%)                                    | 175 (6.1%)                                    | 1.51 (1.20-1.93)     | 1.48 (1.17-1.88)             |
| Country of birth, n (%)                    |                          |                                               |                                               |                      |                                |
| Nordic                                     | 483 (7.5%)               | 184 (9.7%)                                    | 299 (6.5%)                                    | 1.43 (1.20-1.71)     | 1.40 (1.17-1.68)             |
| Non-Nordic                                 | 48 (8.0%)                | 22 (11.3%)                                    | 26 (6.4%)                                     | 1.68 (0.97-2.91)     | 1.63 (0.97-2.92)             |

| Sensitivity analyses                       |                          |                                               |                                               |                      |                                |
| Modified exposure window                   |                          |                                               |                                               |                      |                                |
| 0–6 months before pregnancy               | 136 (10.5%)              | 395 (6.8%)                                    | 1.49 (1.24-1.79)                               | 1.44 (1.20-1.74)     |
| During pregnancy                           | 268 (10.8%)              | 263 (5.8%)                                    | 1.79 (1.51-2.11)                               | 1.71 (1.45-2.02)     |

CI, confidence interval; CD, Crohn’s disease; IBD-U, IBD-unclassiﬁed; UC, ulcerative colitis.  †Clinical IBD activity deﬁned as IBD-related surgery, hospitalization, or IBD medication as detailed in Supplementary Table S7, or without these features regarded as clinically quiescent IBD.  ‡Clustered on the identity of the woman.  §Clustered on the identity of the woman and adjusted for maternal age at delivery, parity, smoking in early pregnancy, body mass index (BMI) in early pregnancy, education, and comorbidity (any diabetes, hypertension, chronic autoimmune disease, and asthma; Supplementary Table S8). The adjusted model failed to converge in speciﬁc analyses (denoted by “#”).  ¶CID: cases for induced preterm delivery include, among others, antepartum haemorrhage and pre-eclampsia.  ¶Extent and location of disease at diagnosis as detailed in Supplementary Table S2.
for preterm birth was confined to women with UC and histological inflammation, particularly extensive colitis. However, histological inflammation was not significantly linked to preterm birth in women with clinically quiescent disease. Our data support recommendations to objectively assess endoscopic and histologic disease remission before conception, to optimize management and prevent adverse outcomes of pregnancy and IBD. This is particularly important against the background that in our IBD cohort (1990–2016), two thirds of biopsied women had histological inflammation and one third had clinical disease activity within 12 months before pregnancy.

Clinical and endoscopic remission are the main therapeutic targets of IBD. However, histological remission may further improve clinical outcomes beyond these therapeutic targets, particularly in UC, where it has been proposed as a potential adjunct treatment goal. Less is known regarding the potential additional prognostic benefits of histological remission in CD, especially outside randomized controlled trials. Overall, there is little data on the long-term prognostic outcomes of histological remission in IBD.

This study links histological inflammation with preterm birth. Excess risks were seen in UC, but not in CD, with the highest risk increase in women with extensive colitis (aRR 2.37; 95%CI 1.12–5.02). Our contrasting UC and CD findings are consistent with previous research showing that a high degree of endoscopic inflammation was linked to hospitalization in UC patients. This association was less evident in CD. Even if histological inflammation was associated with an overall modest risk increase for preterm birth (aRR in our primary analysis was 1.46 [95%CI 1.03–2.06]), its impact on a child’s health can be substantial as preterm birth is a major cause of death in children younger than 5 years. Preterm birth also increases the risk of health sequelae in adulthood. Recent data from the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes study found infants to women exposed to corticosteroids during pregnancy (suggesting more active disease) to be at greater risk of serious infections at 9 and 12 months of age, potentially mediated through preterm birth.

In our study, aRRs for spontaneous preterm birth were only slightly lower than preterm birth overall, indicating that this association is not merely explained by preterm labour induction. Indeed, considerable data implicate inflammation in the pathogenesis of preterm birth, further underlining the need to control histological and clinical disease activity in IBD to minimize the impact on maternal and foetal health. To what extent the association between histological inflammation and preterm birth might have been mediated through anti-inflammatory medication was beyond the scope of this study. A multi-centre study recently observed a link between corticosteroid use and preterm birth in women with IBD. However, we found the association between histological inflammation and preterm birth to be largely similar among women with or without use of corticosteroids. On the other hand, histological inflammation was not significantly linked to preterm birth in women with clinically quiescent disease suggesting that part of the association of histological appearance with preterm birth was related to disease activity.

We and others have reported that approximately one in three IBD women have clinical disease activity soon before pregnancy and demonstrate, consistent with previous studies, that those women have an increased risk of caesarean section, especially elective caesarean section. The current study adds to existing literature, however, by showing that the association with caesarean section is not restricted to disease activity defined by self-reports or inpatient care; nor is our study likely to suffer from confounding from smoking and BMI that may have hampered some studies. Guidelines recommend caesarean delivery to be primarily dictated by obstetric necessity and to limit elective caesarean section to specific IBD phenotypes (e.g., active rectal-perianal involvement or rectovaginal fistula). Still, women with active IBD may have been
recommended caesarean delivery more often than women with quiescent disease. We could not confirm or refute a small excess risk for emergency caesarean section in women with histological inflammation (aRRR 1.22 [95%CI 0.95–1.56]). This is noteworthy as an emergency, but not elective caesarean section, is usually performed for foetal rather than maternal reasons.

We exploited population-based histopathology data as an objective measure of disease activity in IBD. More than 1800 births to women with IBD biopsied <12 months before pregnancy were identified. Earlier validations have shown a positive predictive value of 93%–95% for our IBD definition,13,14 and the validity for the covariates used in our statistical model retrieved from the NPR is high.12 The prospective data collection eliminates recall bias. Through linkage to data on hospital admission, validated IBD surgery data,14 and medication use to estimate clinical disease activity, we could examine the association between histological inflammation and adverse pregnancy outcomes in the absence of clinical IBD activity. Other strengths include using the well-characterized data from the Medical Birth Register, and linkage to other national registers virtually guarantee a complete follow-up of individuals. Finally, we were able to calculate absolute risks (i.e., proportion of events), which are essential in planning health care and communicating risks.

This study has several limitations. As in any observational study, causality cannot be inferred. However, a study randomizing pregnant women (or women desiring pregnancy) to histological or clinical disease activity would be unethical and unlikely to be performed. Thus, while we adjusted for the potential confounding of maternal age, education level, comorbidities, smoking, BMI, and birth country, we recognize that residual confounding cannot be ruled out. Furthermore, the consistency in our findings across patient subgroups, defined by age and calendar year of diagnosis, does not support confounding by indication, i.e., an association related to the indication for biopsy (e.g., cancer surveillance, change in therapeutic management) as a sole cause of our findings.

Another limitation is the lack of data on the clinical indication, symptoms and biomarkers, that could have prompted the histological assessment of IBD. However, women with histological inflammation vs histological remission were more likely to have features of clinically defined disease activity, such as prior IBD-related surgery or hospitalization (Table 1), which suggest that the histological assessment was at least partly related to evaluation and management of disease activity. Another shortcoming is that we did not report whether pregnancy outcomes vary by endoscopic or biochemical remission data. Hence, it is unknown to what extent the association between histological inflammation and preterm birth is explained by the endoscopic appearance of IBD, although we believe that a vast majority of individuals with histological inflammation also have endoscopic inflammation. Furthermore, because histological assessment was not routinely performed before pregnancy, such data were unavailable for all pregnant women. Still, our nationwide approach is likely to have identified all eligible IBD women with a pre-pregnancy histological assessment and reduces the risk of selection bias. Also, comparisons of patient characteristics and pregnancy outcomes of all IBD women under study with those undergoing histological assessment suggest representativeness.

We acknowledge that clinical IBD activity defined by IBD-related hospitalization, surgery, or medication escalation may identify patients with moderate-to-severe disease activity. Patients without these features may not have reached complete clinical or endoscopic remission. Similarly, we recognize that routine histological assessments may not capture the full burden of IBD activity, above all in CD patients, where intramural or segmentally distributed intestinal inflammation may be misclassified as histological remission. In addition, UC patients may be histologically misclassified given that microscopic activity can vary within and across colonic segments, especially after therapy. Finally, in this nationwide study, misclassification may also be related to interobserver variability between clinical pathologists. Importantly, however, the prospective nature of this study ensures that any misclassification of histopathological data should be unrelated to pregnancy outcome. While such non-differential misclassification may attenuate risk estimates, it is unlikely to cause spurious associations. Our data originate from Sweden, a high-income country of mainly Caucasian people with a high incidence of IBD. The generalizability of our findings to other countries is unknown.

Using nationwide prospectively collected data, we showed that histological inflammation in IBD, particularly UC, was associated with an increased risk of preterm birth. While our results suggest that targeting histological remission of women with UC may reduce the risk of preterm birth, further research is needed to determine the importance of pre-pregnancy histological appearance in women without clinically defined disease activity.

Contributors
JFL and OO designed the study, collected study data and are responsible for data integrity. JS analysed the data. JFL, JS, and OO had full access to all the data in the study and verified the underlying data for our results. KM and JFL wrote the first draft of the paper. JS, OS, JA, JH, GB, JM, and OO contributed to the writing of the paper. KM, JFL, and OO obtained funding. JFL supervised the project and is the guarantor of the article. KM, JS, OS, JA, JH, GB, JM, OO, and JFL interpreted the data, agreed with the manuscript’s results and conclusions, approved the final version of the paper and accepted responsibility to submit it for publication.

Data sharing statement
No additional data are available due to Swedish regulations.
Declaration of interests

Dr Ludvigsson has coordinated an unrelated study on behalf of the Swedish Quality Registry for IBD (SWIBREG). That study received funding from the Janssen corporation.

Dr Olén has been PI for projects (unrelated to the current paper) at Karolinska Institutet financed by Janssen, Takeda, AbbiVie, Ferring, and Pfizer grants. Karolinska Institutet has received fees for lectures (OO) and participation on advisory boards (OO) from Janssen, Ferring, Bristol Myers Squibb, Galapagos, and Takeda.

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