Adverse pregnancy outcomes among women with inflammatory bowel disease: A population based study from England

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Abstract

Background

There is limited contemporary population based evidence on adverse birth outcomes and pregnancy related complications for women with inflammatory bowel disease (IBD). This study provides such estimates of these risks and assesses variation by IBD type and surgical interventions.

Methods

We calculated the proportion of pregnancies in women with and without IBD between 1997 and 2012 throughout England using linked primary (Clinical Practice Research Datalink-CPRD) and secondary care (Hospital Episode Statistics-HES) data. Risk of pregnancy related complications and adverse birth outcome in women with Crohn's Disease-CD and Ulcerative Colitis-UC were compared to risks in women without IBD using odds ratios (OR).

Results

Of 364,363 singleton pregnancies resulting in live or stillbirths 1,969 (0.5%) were in women with IBD. Women with CD were more likely to have pre-term births (OR=1.42 95%CI;1.12-1.79), babies with low birth weights (OR=1.39;1.05-1.83) and postpartum haemorrhage (OR=1.27;1.04-1.55) whereas women with UC were only at increased risk of pre-term births with an absolute risk difference of <2.7%. These risks remained independent of caesarean section (CS). Prior surgery for IBD did not increase risk of adverse birth outcomes or pregnancy related complications compared to cases without surgery, however women with IBD were more likely to have an elective CS.

Conclusion

Women with CD, have increased risks of some specific pregnancy related complications and adverse birth outcomes which are independent of caesarean section, however the absolute risk differences are small indicating that most women with IBD will have an uncomplicated pregnancy.

Keywords: inflammatory bowel disease, adverse birth outcomes

Introduction

The incidence of inflammatory bowel disease (IBD) peaks around women's reproductive age and it has been linked to increased risks of pre-term birth and low birth weight which may lead to perinatal mortality.[1] However the results from previous studies are inconsistent perhaps because most have been inadequately powered to provide reliable or precise figures.[2-6] Even a meta-analysis by Cornish et.al[7] which found 97% and 34% relative increases in the risk of pre-term births among those diagnosed with Ulcerative Colitis (UC) and Crohn's Disease (CD) respectively only included 1831 births to mothers with UC and 1005 to mothers with CD. This meta-analysis also reported a statistically significant 3-fold increase in the incidence of low birth weight among the children of mothers with CD compared to non-IBD controls, though there was no significant increase in low birth weight for children of mothers with UC. It is also not clear how adverse birth outcome varies by various mode of deliveries among women with IBD which may be medically driven because of complications related or unrelated to IBD. Furthermore, of studies that have found a significant positive association between IBD and caesarean section[3, 5-8] most were unable to distinguish between the types of caesarean section (emergency versus elective). Finally, the potential impact of prior surgical intervention among women with IBD on these pregnancy outcomes also remains unknown. Accurate estimates of the risk of adverse birth outcomes and pregnancy related complications that are generalizable to the majority of pregnancies in women with IBD will aid both women and practitioners in better decision making. Therefore the aim of this study was to look at the contemporary risk of pregnancy associated complications and adverse birth outcomes among women diagnosed with IBD and assess its variation by IBD type and surgical intervention.

Method

Study population

We used the Clinical Practice Research Datalink (CPRD) [9] which is a large longitudinal UK database that contains the anonymised primary care records of patients in computerised form. The CPRD includes practices where staff have been trained to enter data to the necessary standard for research, and identifies the date at which this standard is reached. All patients within a participating practice are automatically included. Data from around 53% of the CPRD practices are also linked to Hospital Episode Statistics (HES)[10, 11] data which contains more detailed information on all hospitalisations in England, including all discharge diagnoses and procedures. As HES only covers English hospitals, practices from Northern Ireland, Wales and Scotland are excluded. The linked portion of the CPRD has been shown to be similar in terms of age and sex distribution to the UK population published by the Office for National Statistics (ONS)[12]. Diagnoses of IBD[13] in primary care and delivery/birth information in HES maternity data[14] have been validated to external sources with positive predictive values of 92% and 93% respectively.

Defining cases

We used as our source population the entirety of CPRD records for practices linked to HES data, during the period for which this linkage was available (1997-2012). Women in this population aged 15-44 years with HES-recorded singleton pregnancies ending in a live birth or a stillbirth between 1997 and 2012 were identified from our study population. Pregnant women were defined as having IBD during pregnancy if they had ever had a diagnosis before delivery or if they had a diagnosis after delivery but a prescription of 5-ASA at some point before delivery. Information on the IBD diagnosis was extracted using both primary and secondary care data. Pregnant women with IBD were classified as having CD if they had

diagnoses specifying this condition regardless of whether they also had diagnoses of UC, as having UC if they had recordings of UC but not CD, and as having unclassified IBD if their coding for IBD did not specify CD or UC.

For pregnant women with IBD, we also extracted information on surgical interventions that included women undergoing small bowel (e.g. excision of lesion of ileum), large bowel (e.g. colectomy), perianal surgery (e.g. Perianal excision lesion of rectum) or pouch surgery (e.g. anastomosis of ileum to rectum) using their both primary and secondary care records (code list available on request). In order to correctly ascertain pouch surgeries among women with UC, we also reviewed their surgical records. We considered women as having surgical intervention for IBD if they had a record for a relevant surgical procedure at any point from diagnosis up to their date of delivery. Our control population was pregnant women without a diagnosis of IBD in their primary or secondary care records.

Defining outcomes

From HES, we extracted information on pregnancy related complications (postpartum haemorrhage, antepartum haemorrhage, gestational diabetes, venous thromboembolism and pre-eclampsia/eclampsia) using previously established methodology.[15, 16] Mode of delivery was categorised as normal vaginal delivery, assisted vaginal delivery (forceps, breech or vacuum), emergency and elective caesarean. We also extracted information on adverse birth outcomes (pregnancies resulting in pre-term births (<37 weeks of gestation), post-term births (>41 weeks), stillbirths or infants born with low birth weight (<2500 grams)).

Defining maternal co-variables

For each pregnancy, information on maternal factors during or before pregnancy was extracted from the patient's medical record. Maternal age at delivery was considered in 5-year age bands. Information on body mass index (BMI) categorised as normal weight ($18.5kg/m^2 \leq BMI<25kg/m^2$), underweight ($BMI<18.5kg/m^2$), overweight ($25kg/m^2 < BMI<30kg/m^2$) and obese ($BMI \geq 30kg/m^2$) using the latest measure recorded by the general practitioner before the date of conception, smoking status categorised as current smoker or non-current smoker using the latest measure recorded by the general practitioner before delivery and ethnicity (as recorded in HES and grouped into white or non-white) was also extracted. Pregnant women were also defined as having diabetes in pregnancy (either pre-existing or gestational) if it was recorded either in primary or secondary care data, or if a woman received a prescription for anti-diabetic medication (insulin or oral hypoglycaemic agents) at any time before delivery.

Statistical analysis

We calculated the proportions of pregnancies affected for all pregnancy related complications and adverse birth outcomes among those with and without IBD. These estimates were then stratified by IBD type (CD or UC) and perianal disease. Since only a small proportion of IBD in pregnant women was unclassified, their segregated results are not presented. We used logistic regression models to calculate the odds ratios (OR) and 95% confidence interval (95% CI) for the associations between IBD diagnosis and pregnancy related complications and adverse birth outcomes. These estimates were adjusted for maternal age, BMI, smoking status, calendar year at delivery (categorised to birth at 1997-2001, 2002-2006 and 2007-2012), diabetes and ethnicity. Missing information on BMI, smoking status and birth weight was grouped into separate categories and included in the analyses. In order to assess the

extent to which the adverse birth outcomes (e.g. pre-term births) were medically driven (via elective caesarean sections), we carried out subgroup analyses among women who underwent normal vaginal or assisted delivery, elective caesarean section, emergency caesarean section and excluding women who underwent elective caesarean section. Similarly, to examine if the association between IBD and low birth weight is independent of the length of gestation, we analysed the risk of low birth weight among women with term births only. Among those diagnosed with IBD (UC or CD), we assessed the association of previous surgery for IBD with the risk of pregnancy related complications and adverse birth outcomes compared to women without such previous surgery. This analysis was then further stratified by disease type (UC and CD) and type of surgery. We also assessed the potential impact of pouch surgery among women with UC on pregnancy outcomes by restricting to those women in our analysis. For the purpose of this study, the categorisation of surgical intervention was not considered as mutually exclusive (i.e. if a woman had undergone more than one type of surgery prior to a pregnancy this was included in the analysis). As we did not have information on the severity of disease, we identified IBD case prescribed steroids at any point in time during pregnancy to assess the impact of disease activity on adverse outcomes. A clustering term was fitted in the models to account for women experiencing more than one pregnancy during the study period. All analyses were carried out using Stata MP 13.0 (Stata Corp., College Station, TX, USA).

Ethical consideration

This study was approved by the CPRD's scientific advisory committee (ISAC) (reference number= 10_193)

Results

Study population

Among 276,719 women in our study population, there were 364,363 singleton pregnancies resulting in a live birth or a stillbirth. The proportion of pregnancies in women who had IBD diagnosed at some point before delivery was 0.5% (n=1,969). The majority (n=1,664 (85%)) of IBD diagnoses were made more than one year before delivery. Of all women with IBD, 51% (n=1,002) had CD and 45% (n=884) had UC with the remainder (n=83, 4%) of cases being of unclassified IBD type. Table 1 shows the maternal characteristics of mothers with and without IBD. Compared to controls, pregnant women with IBD were slightly older and more likely to be underweight particularly those with CD. Those with UC had a higher prevalence of diabetes and were less likely to be smokers compared to the control population whereas women with CD were more likely to be smokers. These differences were statistically significant (p-value <0.01). Overall, we found modestly increased risks of pregnancy related complications and adverse birth outcomes among pregnant women with IBD compared to the control population (Table 2). The risk for gestational diabetes, pre-eclampsia/eclampsia, pre-term birth and low birth weight was further increased among cases prescribed steroids during pregnancy (supplementary table 1).

Adverse pregnancy and birth outcome among CD

The absolute risks of antepartum and postpartum haemorrhages among those with CD were 5.2% and 12.3% respectively. This corresponded to a 0.5% and 2.6% absolute excess risk respectively compared to the control population (Table 2). Compared to controls, women with CD were more like to undergo elective caesarean section with an absolute risk of 17.2% vs 9.7%, i.e. almost 2-fold (Adjusted odds ratio (AOR)=1.97; 95%CI 1.61-2.40) whereas the increase was more modest for emergency caesarean section (AOR=1.31; 95%CI 1.08-1.59)

(Table 3). Higher risk of assisted deliveries (AOR=2.61; 95%CI 1.50-4.53) and elective caesarean section (AOR=6.20 95%CI 3.82-10.04) was observed for those with perianal crohn's compared to controls. We did not find CD to be associated with a higher risk of stillbirths; however women with CD were 42% (AOR=1.42; 95%CI 1.12-1.80) and 40% (AOR=1.40 95%CI 1.06-1.85) more likely to deliver pre-term (gestation<37 weeks) and have smaller babies (birth weight<2500 grams) respectively compared to the control population. Even among women with CD delivering at term, we found an increased risk of having babies with low birth weight, although the association was not statistically significant (AOR=1.37 95%CI 0.92-2.04). We also found that mothers with CD had babies with a mean weight 80 grams lower (95%CI -40 to -120) compared to those without IBD. Finally the positive associations observed between CD and postpartum haemorrhage, pre-term birth and low birth weight remained when we excluded pregnant women who underwent caesarean section (Figure 1) and excluded CD cases with perianal disease (supplementary table 2).

Adverse pregnancy and birth outcome among UC

Among pregnant women with UC, we did not observe a significantly increased risk of antepartum haemorrhage, postpartum haemorrhage, pre-eclampsia/eclampsia or emergency caesarean section compared to women without IBD (Table 2). The absolute rate of elective caesarean section was higher among those with UC compared to controls (13.7% versus 9.7%); however this increased risk was not statistically significant (Table 2 and Table 3). We observed that women with UC were 33% more likely to have pre-term births (AOR=1.33 95%CI 1.06-1.67, absolute risk 8.5% in UC vs 6.5% in controls). This effect was also statistically significant when we excluded women who underwent caesarean sections (Figure 2). Finally, pregnant women with UC were not at a higher risk of stillbirths or giving birth to babies with low birth weight. There was also no statistically significant difference in the

mean birth weight among cases and controls (Mean difference=-28 grams 95%CI -13 to 70) (Table 2).

Surgical intervention for IBD and adverse pregnancy and birth outcomes

Some form of surgical intervention for IBD occurred before 344 (17.4%) of the deliveries. We found no increased risk of pregnancy related complications and adverse birth outcomes occurring in pregnancies following surgical intervention compared to those with IBD without surgical intervention (Table 4). However, those who underwent any surgical procedure for IBD were 3 times more likely to undergo elective caesarean section (absolute risk=28.5%; AOR=3.15 95%CI 2.23-4.45) compared to those IBD cases without any surgical intervention (absolute risk=12.4%).

For CD, our results for postpartum haemorrhage, mode of delivery and length of gestation remained broadly similar when we stratified our analysis by type of surgery except for perianal surgery which was associated with a 4-fold (AOR=4.27 95%CI2.38-7.68) increase in risk of elective caesarean section (Supplementary table 3). Women with UC who under-went surgical intervention were 13 times (Absolute risk=51% AOR=13.01 95%CI 5.68-29.80) more likely to undergo elective caesarean section compared to those without surgical intervention. This association was even stronger when we restricted our analysis to those who underwent pouch surgery (Supplementary table 4).

Discussion

Main findings

In this large cohort study of more than 360,000 singleton pregnancies resulting in a live birth or a stillbirth, we have provided population-based estimates of the proportion of such pregnancies complicated by IBD that have pregnancy related complications and adverse birth outcomes. Around 0.5% of these pregnancies were among women who have IBD, of which more than half had CD. Women with CD were at increased risk of postpartum haemorrhage, caesarean section, pre-term birth and low birth weight compared to those without an IBD diagnosis with the absolute excess risk ranging between 1.6% (low birth weight) and 2.6% (pre-term birth). Given baseline risks of 4.5% low birth weight and 6.5% preterm birth in the general population (without IBD), these increases are modest. Women with CD were also more likely to undergo both elective and emergency caesarean sections. The increased risk of pre-term birth and low birth weight among women with CD remained when we excluded women who underwent caesarean section. In contrast, those with UC were only at an increased risk of pre-term delivery and this association remained statistically significant when we excluded those who underwent caesarean section delivery. We found no increased risks of pregnancy related complications and adverse birth outcomes among those with prior surgical intervention for IBD compared with those with IBD but without a history of surgical intervention. However, there was an increased risk of elective caesarean section associated with a history of surgical intervention which was more apparent in the UC group.

Strengths and limitations

We have conducted one of the largest single studies yet to determine the risk of pregnancy related complications and adverse birth outcomes in women with IBD. Our study used an open cohort approach, with prospectively collected data and utilised information from linked

primary and secondary care data sources from across England covering 3% of the total UK population with a similar age and sex distribution to the population as a whole.[17] Our study findings should therefore not only be generalisable to singleton pregnancies resulting in a live birth or a stillbirth in England but also to other developed nations with similar health care systems and baseline incidence of adverse outcome. As HES is the primary source of maternity statistics in England and its birth outcomes have been externally validated with high accuracy,[14] we believe that under recording of birth outcomes and differential recording of adverse pregnancy related complications/outcomes between women with and without diagnosed IBD is unlikely. Our use of linked data from both primary and secondary care also allows better adjustment for important confounding factors such as BMI, smoking status and maternal diabetes.

A potential weakness of this study is that since we used anonymised patient records and had no direct access to the patients, we were dependent on family doctors entering data accurately in CPRD. However, the diagnosis of IBD has been previously validated in UK electronic general practice data with a high degree of accuracy so we think it unlikely that there is major error in our findings due to misattribution of the diagnosis of IBD.[13] We also acknowledge that there are other commonly investigated outcomes (spontaneous abortion, APGAR score and neonatal death) which we were not able to assess in our study due to the lack of complete and reliable data. However, previously our group found very limited increased risk of major congenital anomalies in children born to mothers with IBD[18] using another similar dataset which had linked mother baby information.

Interpretation in the context of previous literature

Our finding of increased risk of pre-term birth among babies born to mothers with CD is consistent with most previous studies although the magnitude of the effect that we observed

in our study was slightly lower than most[2, 4-6] but not all previous studies.[19-21] It should be noted that the greatest apparent magnitudes (more than 2-fold increased risk compared to controls) for this association have been in general reported by small often single centre studies[2, 4-6] based on 38 to 177 cases. However, the few large multicenter population based studies with more than 500 cases are more similar in their findings to our own.[19, 20, 22] Similarly, our finding of an increased risk of having babies with low birth weight among CD mothers is in line with the existing literature.[19, 20] We showed that pregnant women with UC are more likely to have pre-term birth compared to the control population whereas the risk of having babies with low birth weight is similar between cases and controls. This finding is supported by a number of previous studies[2, 4, 23] and a meta-analysis.[7] In contrast, Dominitz et al[5] in their multicenter hospital based study, found no association between prematurity and UC which may be due to the database and methodology used to define their exposure. For instance, the authors established the presence or absence of IBD through the review of diagnoses listed in the discharge record from hospitalisation associated with birth leading to under ascertainment of IBD cases. This is evident by their much lower prevalence of IBD in pregnancy (0.03%) compared to our own (0.5%). Moreover, the IBD definition was not validated in this previous study which may have led to misclassification between CD and UC given that the study also reported a much higher increased risk (4-fold) of pre-term birth associated with CD. Similarly, Bortoli et al[21] found no evidence of pre-term birth among those with UC or CD which may be attributed to their small number of cases and high dropout rate which may have biased their estimates. Our stratified analyses by mode of delivery show evidence that prematurity and babies born with low birth weight observed among IBD cases may be independent of factors and/or complications leading to medically driven caesarean section for which further studies are needed.

Our finding of higher proportions of women with IBD undergoing caesarean sections particularly among those with CD is not new and has been previously demonstrated.[24] Of interest is the fact that the majority of the caesarean sections were elective. Whilst clinical guidelines[25, 26] only support caesarean section delivery among those with complicated IBD (those with severe disease, with perianal disease and some women with pouches) and the risk of readmissions post-caesarean sections are higher compared to those who undergo normal vaginal delivery,[27] controversies exist over the most appropriate mode of delivery among pregnant women with IBD. For instance, there is evidence suggesting that the risk of incontinence and sphincter tear is greater among those who undergo normal vaginal delivery than in caesarean section.[7] On the other hand there is evidence suggesting that refraining from vaginal delivery does not necessarily protect against incontinence[28] and that vaginal delivery does not seem to substantially influence pouch function and quality of life.[29] Presumably, previous abdominal surgery affects the choice of delivery method by both the woman and clinicians involved in their antenatal care as our study demonstrated that a higher proportion of women who had prior surgery for IBD underwent elective caesarean sections. This effect was more prominent among those with UC even after excluding women who had pouch surgery. In order to better understand the relationship between caesarean section and IBD, it may be important to explore the primary indication for caesarean section (IBD versus other medical causes) for which we do not have data.

We found that among those who underwent surgical intervention prior to delivery, there was no increased risk of adverse birth outcomes compared to those with IBD without surgical intervention. Whilst these findings may be reassuring, Stephansson et al[20] reported a more than 53% increased risk of pre-term birth among Swedish and Danish pregnant women with a history of CD related surgery. This may be due to the fact that this previous study was based

on inpatient registry data with limited information on outpatient visits. Therefore their cases may be more likely to be those with moderate to severe disease leading to slight overestimation of the actual risk. In contrast our study provides a more representative picture of IBD with disease severity ranging from mild to severe.

Our finding of increased risk of postpartum haemorrhage among those with CD contradicts the findings of Broms et al.[24] This may be due to the difference in study design and population studied. For instance, postpartum haemorrhage is more common in the UK compared to Sweden (10% versus 6%). Additionally, there is also a marked difference between the incidences of caesarean sections between the two counties (17% in Sweden versus 26% in the UK) which may be a contributory factor. Our increased risk observed for postpartum haemorrhage was however independent of caesarean section.

In conclusion, women with CD are at increased risk of pre-term birth, low birth weight and postpartum haemorrhage independent of any effect that either IBD or its complications have in increasing caesarean section among these women. In contrast women with UC are only at higher risk of pre-term births and for all IBD there was no association with stillbirth. Whilst IBD related surgery itself is not associated with the risk of adverse pregnancy related complications, it is may be considered an important factor in the decision for elective caesarean section especially among those with UC. These findings should be carefully considered by women with IBD planning pregnancy and when in clinical consultation with pregnant women with IBD. Despite the fact that we have shown significantly increased risks for certain pregnancy related complications and adverse birth outcomes particularly among those with CD, the absolute differences are small indicating that most women with CD and UC will have an uncomplicated pregnancy ending in favourable outcomes.

Tables

Table 1: Descriptive data on singleton births among women diagnosed with inflammatory bowel disease and the control population

Variable	Pregnancies among women not diagnosed with IBD (N=362,394)		Pregnancies among women diagnosed with IBD (N=1,969*)		Pregnancies among women diagnosed with CD (N=1,002)		Pregnancies among women diagnosed with UC (N=884)	
	No.	%	No.	%	No.	%	No.	%
Age at delivery**								
15-19 years	21,218	5.9	22	1.1	17	1.7	4	0.5
20-24 years	62,195	17.2	181	9.2	117	11.7	51	5.8
25-29 years	95,506	26.4	475	24.1	269	26.8	191	21.6
30-34 years	110,442	30.5	725	36.8	360	35.9	334	37.8
35-39 years	60,725	16.8	452	23.0	194	19.4	239	27.0
40-44 years	12,308	3.4	114	5.8	45	4.5	65	7.4
Body Mass Index**								
Normal(18.5-24.9)	157,950	43.6	1,001	50.8	486	48.5	461	52.1
Underweight(<18.5)	11,807	3.3	76	3.9	43	4.3	32	3.6
Overweight(25-29.9)	65,585	18.1	350	17.8	183	18.3	151	17.1
Obese(>=30)	41,036	11.3	198	10.1	115	11.5	76	8.6
Missing	86,016	23.7	344	17.5	175	17.5	164	18.6
Smoking status**								
Current smoker	79,650	22.0	370	18.8	257	25.6	97	11.0
Non-smoker	282,744	78.0	1,599	81.2	745	74.4	787	89.0
Ethnicity**								
White	263,716	72.8	1,629	82.7	847	84.5	713	80.7
Non-white	37,127	10.2	101	5.1	50	5.0	49	5.5
Missing	61,551	17.0	239	12.1	105	10.5	122	13.8
Diabetes								
No	351,752	97.1	1,903	96.6	980	97.8	843	95.4
Yes	10,642	2.9	66	3.4	22	2.2	41	4.6
Calendar year at birth**								
1997-2001	72,829	20.1	334	17.0	187	18.7	132	14.9
2002-2006	126,865	35.0	658	33.4	339	33.8	294	33.3
2007-2012	162,700	44.9	977	49.6	476	47.5	458	51.8

*Includes Crohn's disease, Ulcerative colitis and non-specific IBD (n=83). **Statistically significant differences between IBD case and controls (p<0.001)

Table 2: Risk of adverse pregnancy and birth outcome among women diagnosed with inflammatory bowel disease

Outcomes	Controls (N=362,394)		IBD cases* (N=1,969)		CD (N=1,002)		UC (N=884)	
	n	%	n	%	n	%	n	%
Pregnancy related complications								
Postpartum haemorrhage	35,197	9.7	229	11.6	123	12.3	97	11.0
Pre-eclampsia/eclampsia	8,261	2.3	41	2.1	24	2.4	15	1.7
Antepartum haemorrhage	17,052	4.7	104	5.3	52	5.2	47	5.3
Venous thromboembolism	567	0.2	8	0.4	3	0.3	5	0.6
Gestational diabetes	6,667	1.9	46	2.4	14	1.4	29	3.3
Mode of delivery								
Normal vaginal delivery	233,222	64.4	1,093	55.5	539	53.8	508	57.5
Assisted	43,846	12.1	278	14.1	137	13.7	128	14.5
Elective caesarean	35,301	9.7	300	15.2	172	17.2	121	13.7
Emergency caesarean	50,025	13.8	298	15.1	154	15.4	127	14.4
Adverse birth outcomes								
Adverse birth outcomes[1]	31,296	8.6	222	11.3	120	12.0	94	10.6
Stillbirth[5]	1,566	0.4	10	0.5	5	0.5	4	0.5
Length of gestation								
Normal (37-41 weeks)	304,870	84.1	1,651	83.8	832	83.0	751	85.0
Pre-term (<37 weeks)	23,525	6.5	170	8.6	91	9.1	75	8.5
Prolonged (>41 weeks)	33,999	9.4	148	7.5	79	7.9	58	6.6
Birth weight in grams								
2500-4500 grams[δ]	272,232	75.2	1,492	75.9	736	73.5	688	77.9
>4500 grams	5,283	1.5	24	1.2	7	0.7	15	1.7
<2500 grams	16,406	4.5	107	5.4	61	6.1	42	4.8
Missing	68,083	18.8	343	17.4	197	19.7	138	15.6
Mean birth weight (SD)	3381	(581)	3331	(587)	3301	(589)	3353	(581)

*Includes Crohn's disease, Ulcerative colitis and non-specific IBD [1]Includes pregnancies of women resulting in stillbirth, pre-term birth or infant born with low birth weight. SD = Standard deviation. [δ]Among live births only

Table 3: Risk of adverse pregnancy and birth outcome among women diagnosed IBD compared to controls stratified by Ulcerative colitis and Crohns disease

Variables	IBD	CD	UC
	OR* (95% CI) Adjusted[1]	OR* (95% CI) Adjusted[1]	OR* (95% CI) Adjusted[1]
Pregnancy complication			
Postpartum haemorrhage	1.16 (1.00-1.34)	1.27 (1.04-1.55)	1.05 (0.84-1.30)
Pre-eclampsia/eclampsia	0.95 (0.68-1.33)	1.11 (0.70-1.75)	0.76 (0.46-1.28)
Antepartum haemorrhage	1.18 (0.97-1.45)	1.14 (0.86-1.51)	1.22 (0.90-1.66)
Venous thromboembolism	2.48 (1.23-5.00)	-	3.49 (1.43-8.47)
Gestational diabetes	1.21 (0.88-1.67)	0.74 (0.37-1.46)	1.64 (1.12-2.40)
Mode of delivery			
Assisted[3]	1.26 (1.10-1.45)	1.31 (1.08-1.58)	1.21 (0.99-1.48)
Elective caesarean[3]	1.56 (1.34-1.81)	1.97 (1.61-2.40)	1.24 (0.99-1.56)
Emergency caesarean[3]	1.20 (1.05-1.38)	1.31 (1.08-1.59)	1.06 (0.86-1.29)
Adverse birth outcomes			
Adverse birth outcomes[4]	1.39 (1.19-1.61)	1.45 (1.18-1.78)	1.33 (1.06-1.67)
Stillbirth	1.23 (0.66-2.29)	1.17 (0.48-2.81)	1.13 (0.42-3.01)
Length of gestation			
Pre-term (<37 weeks)[5]	1.36 (1.15-1.61)	1.42 (1.12-1.80)	1.34 (1.04-1.73)
Prolonged (>41 weeks)[5]	0.82 (0.69-0.97)	0.85 (0.67-1.07)	0.73 (0.55-0.95)
Birth weight			
>4500 grams[6]	0.75 (0.49-1.15)	0.45 (0.21-0.95)	1.01 (0.58-1.74)
<2500 grams[6]	1.27 (1.03-1.56)	1.40 (1.06-1.85)	1.14 (0.82-1.59)
Missing[6]	0.99 (0.87-1.12)	1.13 (0.95-1.34)	0.89 (0.73-1.08)

[1]Adjusted for smoking status, age, ethnicity, diabetes, calendar year and BMI
[2]Analysis based on pregnancies not resulting in normal vaginal delivery as the comparison group
[3]Analysis based on normal vaginal delivery as the comparison group
[4]Includes pregnancies of women resulting in stillbirth, pre-term birth or infant born with low birth weight
[5]Analysis based on pregnancies with normal gestational length (37-41 weeks)
[6]Analysis based on pregnancies resulting in live births with baby's weight between 2500-4500 grams

Table 4: Risk of adverse pregnancy and birth outcome among women diagnosed with inflammatory bowel disease with surgery prior to the pregnancy compared women without prior surgical intervention

Outcome	Pregnancies of women with no surgical intervention for IBD before delivery (n=1,625)		Pregnancies of women after surgical intervention for IBD before delivery (n=344)		OR (95% CI) (Adjusted[1])
	No.	%	No.	%	
Pregnancy related complications					
Postpartum haemorrhage	186	11.4	43	12.5	1.10 (0.76-1.59)
Antepartum haemorrhage	88	5.4	16	4.7	0.86 (0.50-1.49)
Pre-eclampsia/eclampsia	32	2.0	9	2.6	1.37 (0.64-2.93)
Venous thromboembolism	-	-	-	-	-
Gestational diabetes	41	2.5	5	1.5	0.59 (0.22-1.59)
Mode of delivery					
Assisted[3]	226	13.9	52	15.1	1.53 (1.06-2.22)
Elective caesarean[3]	202	12.4	98	28.5	3.15 (2.23-4.45)
Emergency caesarean[3]	247	15.2	51	14.8	1.33 (0.91-1.94)
Birth outcome					
Adverse birth outcome[4]	181	11.1	41	11.9	1.07 (0.74-1.56)
Still birth	8	0.5	-	-	-
Length of gestation					
Pre-term (<37 weeks)[5]	137	8.4	33	9.6	1.16 (0.74-1.67)
Prolonged (>41 weeks)[5]	121	7.4	27	7.8	1.05 (0.67-1.64)
Birth weight					
>4500 grams[6]	18	1.1	6	1.7	1.54 (0.53-4.44)
<2500 grams[6]	86	5.3	21	6.1	1.20 (0.70-2.04)
Missing[6]	287	17.7	56	16.3	0.-94 (0.67-1.30)

[1]Adjusted for smoking status, age, ethnicity, diabetes, calendar year and BMI
[2]Analysis based on pregnancies not resulting in normal vaginal delivery
[3]Analysis based on normal vaginal delivery
[4]Includes pregnancies of women resulting in stillbirth, pre-term birth or infant born with low birth weight
[5]Analysis based on pregnancies with normal gestational length (37-41 weeks)
[6]Analysis based on pregnancies resulting in live births with baby's weight between 2500-4500 grams
- <3 cases omitted.

Figure legends

Figure 1: **Risk of adverse pregnancy and birth outcome among women diagnosed CD compared to controls stratified by the mode of delivery (log_{10} scale).**

Figure 2: **Risk of adverse pregnancy and birth outcome among women diagnosed UC compared to controls stratified by the mode of delivery on (log_{10} scale).**

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Study Contributions

AAS and TC conceived the idea for the study, with all authors also making important contributions to the design of the study. AAS carried out the data management and analysis and wrote the first draft of the manuscript. All authors were involved in the interpretation of the data, contributed towards critical revision of the manuscript and approved the final draft. AAS had full access to all of the data and final responsibility for the decision to submit for publication.

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