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Mode of child-birth and long-term outcomes in women with inflammatory bowel diseases

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Abstract

Introduction: Inflammatory bowel diseases (IBD; Crohn's disease (CD), ulcerative colitis (UC)) often affect women in their reproductive years. Few studies have analyzed the impact of mode of child-birth on long-term IBD outcomes.

Methods: We used a multi-institutional IBD cohort to identify all women in the reproductive age group with a diagnosis of IBD prior to pregnancy. We identified the occurrence of a new diagnosis code for perianal complications, IBD-related hospitalization and surgery, and initiation of medical therapy after either a vaginal delivery or caesarean section (CS). Cox proportional hazards models

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adjusting for potential confounders was used to estimate independent effect of mode of child-birth on IBD outcomes.

Results: Our cohort included 360 women with IBD (161 CS). Women in the CS group were likely to be older and more likely to have complicated disease behavior prior to pregnancy. During follow-up, there was no difference in the likelihood of IBD-related surgery (multivariate hazard ratio 1.75, 95% confidence interval (CI) 0.40 – 7.75), IBD-related hospitalization (HR 1.39), initiation of immunomodulator therapy (HR 1.45) or anti-TNF therapy (HR 1.11). Among the 133 CD pregnancies with no prior perianal disease, we found no excess risk of subsequent new diagnosis perianal fistulae with vaginal delivery compared to CS (HR 0.19, 95% CI 0.04 – 1.05).

Conclusions: Mode of delivery did not influence natural history of IBD. In our cohort, vaginal delivery was not associated with increased risk of subsequent perianal disease in women with CD.

Keywords

Crohn's disease; ulcerative colitis; pregnancy; delivery; caesarean section

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic immunologically mediated diseases with a peak incidence for both Crohn's disease (CD) and ulcerative colitis (UC) occurring during the 2nd-4th decades of life^{1, 2}. Owing to its protracted lifelong course characterized by periods of remission and relapse, many women with IBD go through their reproductive years with concerns about the impact of disease on pregnancy outcomes, and conversely about the impact of pregnancy and childbirth on their disease. Despite the growing wealth of literature on this topic, significant gaps in knowledge and perception remain³⁻⁵. Most prior studies in this area have focused on fertility and fecundity, effect of the pregnancy itself on course of IBD during pregnancy and the immediate post-partum period, and the effect of IBD on pregnancy outcomes including gestational age and birth weight⁶⁻¹⁵. Reassuringly, apart from a weak increase in incidence of preterm births and low birth weight babies, neither CD nor UC are associated with other adverse pregnancy or health outcomes⁶⁻¹⁵. Furthermore, most of the current medications for treatment of IBD may be safely continued during pregnancy and in the post-partum period^{10, 16-18}.

The recent decades have witnessed a significant increase in the proportion of women delivering via caesarean section (CS)¹⁹⁻²¹. Those with IBD seem to be at 1.5-2 fold increase in likelihood of childbirth via CS^{9, 13, 22, 23}. This increase does not appear to be solely due to obstetric indications and is likely influenced in part by patient and provider preferences. One plausible reason for this preference towards operative delivery is the concern regarding perineal trauma during vaginal childbirth in those with established IBD, particularly those with CD who may be prone towards development of perianal disease with their CD. The data in this area, both incidence of new diagnosis of perianal involvement as well as outcomes of perianal fistula in those with established perianal CD, is limited both in the number of patients studied as well as the methods employed with biases stemming from self-report, small cohorts, or short duration of follow-up²⁴⁻²⁷. Thus, larger cohorts examining the effect of mode of delivery on long-term outcomes of women with CD or UC

are important to provide objective and accurate estimates on relative safety of the two modalities of childbirth.

Using a large multi-institutional IBD cohort, we identified all women who had childbirth at one of two tertiary referral IBD centers. We examined the impact of mode of delivery on IBD outcomes over a median follow-up of 4 years.

METHODS

Study Cohort

Our study cohort included data from women seeking care at two major tertiary centers in Boston (Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH)) and affiliated medical centers comprising the Partners Healthcare network. The two hospitals together serve over 3 million patients in the greater Boston metropolitan area and serve as referral centers. The development of our IBD cohort has been described in detail in previous publications²⁸⁻³³. In brief, we first identified all patients with at least one International Classification of Diseases, 9th edition, clinical modification (ICD-9-CM) codes for CD (555.x) or UC (556.x). Using a combination of codified data for diagnoses and procedures, free text concepts identified using natural language processing from office visit notes, discharge summaries, pathology, laboratory, and radiology reports, endoscopy findings, and operative reports, and medication use determined using electronic prescription data from the medical record, we developed and validated an algorithm that defined CD or UC with a positive predictive value of 97%. This yielded a final IBD cohort of 5,522 UC and 5,506 CD patients³⁰.

For the purpose of this study, we identified all women with IBD who had at least one pregnancy and delivery at our institutions (n=497). Women with codes for vaginal delivery (ICD-9-CM 650, 660-669) comprised the vaginal delivery group while those who underwent delivery via caesarean section comprised the CS group (ICD-9-CM 669.7, 74.0-74.9). If patients had codes for both on the same day, they were assigned to the CS group. Only deliveries occurring after the first diagnosis code for CD or UC were included in this analysis resulting in a final cohort of 360 women. Only the first pregnancy after diagnosis of IBD was included in the analysis. Spontaneous abortions were not included in the analysis.

Variable definition

Information was recorded about age at pregnancy and age at first diagnosis code for CD or UC, disease duration (interval since first diagnostic code for CD or UC) at pregnancy, race, and type of IBD. Among those with CD, complicated disease phenotype was defined by the presence of codes for stricturing or penetrating complications (**Supplementary Table**). As well the presence of codes for perianal fistula, anorectal strictures, or perianal surgery was noted separately. The use of immunomodulators (azathioprine, 6-mercaptopurine (6-MP), methotrexate) and monoclonal antibodies to tumor necrosis factor α (anti-TNF) (infliximab, adalimumab, and certolizumab pegol) were defined both prior to and following pregnancy using the electronic prescription function of our medical record.

Outcomes

Our primary study outcomes included the following: - (i) new prescriptions for immunomodulator or anti-TNF therapy after pregnancy (in prior non-users); (ii) IBD-related hospitalizations defined as those hospitalizations where IBD was determined to be primary diagnosis on discharge, and (iii) an IBD-related bowel resection surgery. Furthermore, among those with CD, we specifically examined the occurrence of a new diagnosis code for perianal fistulizing disease or perianal surgical procedures in those with no such codes prior to pregnancy.

Statistical Analysis

All statistical analysis was performed using Stata 12.0 (StataCorp, College Station, TX). Continuous variables were summarized using medians and inter-quartile ranges (IQR) while categorical variables were expressed as proportions and compared using the chi-square test. All patients contributed person-time from the date of delivery (vaginal or CS) until the subsequent pregnancy, occurrence of one of our study outcomes, end of follow-up in our health system, or death. Kaplan-Meier survival curves were constructed to compare time to occurrence of events, stratifying by mode of childbirth and differences compared using the log-rank test. Cox proportional hazards models defined the independent effect of the mode of childbirth (vaginal delivery vs. CS), adjusting for other relevant covariates in the model. All survival models satisfied the proportional hazards assumption.

As choice of mode of delivery is a non-random occurrence and is likely influenced by severity of prior disease and phenotype, we additionally performed a propensity score adjusted analysis. We first calculated a propensity score that predicted likelihood of delivery via CS based on age, duration of disease, IBD type, prior medical therapy, IBD-related surgery, perianal disease, or disease phenotype (penetrating or stricturing complications). The propensity score performed well in differentiating those likely to delivery vaginally from those who delivered via CS ($p < 0.0001$). In addition to the unadjusted hazard ratio (HR), we calculated the HR and 95% confidence intervals (CI) for models additionally adjusting for the propensity score, and a multivariate model adopting traditional methods incorporating variables that met statistical significance on the univariate analysis ($p < 0.05$) or were deemed to be clinically relevant based on existing literature. The study was approved by the Institutional Review Board of Partners Healthcare.

RESULTS

Our IBD cohort included 2,702 women between the ages of 18-45 years (1,320 UC, 1,382 CD) among whom 497 women had at least one successful term pregnancy at our institution. A total of 137 women had a pregnancy before the first diagnosis code for CD or UC and were excluded, leaving 360 women available for analysis. Among these, 161 delivered through CS and 198 had a vaginal delivery. **Table 1** compares the characteristics for women across the two modes of delivery. Women in the CS group were slightly older (mean age 33.5 years vs. 32.1 years) but were similar to the vaginal delivery group in race and distribution of IBD. The patients had a mean follow up of 2 years (interquartile range (IQR) 1-5 years) at our center prior to their pregnancy, and had a post-pregnancy follow-up of 4

years (IQR 2–8 years). Among women with CD, those with prior perianal disease (20% vs. 8%) or complicated disease behavior (21% vs. 5%) were more likely to delivery via CS than vaginally ($p < 0.05$ for both comparisons). There was no difference in medical therapy prior to pregnancy across both groups though the CS group was more likely to have a prior IBD-related surgery (9% vs. 4%, $p=0.02$).

Table 2 presents the results of unadjusted and adjusted models comparing the various outcomes between the vaginal delivery and the CS groups. Ninety-nine (99/199, 50%) patients had a subsequent IBD-related hospitalization after pregnancy among the vaginal delivery group compared to 65/161 (40%) in the CS group (HR for vaginal delivery compared to CS 1.20, 95% CI 0.87 – 1.64). The difference between the two groups remained non-significant in both the propensity score adjusted model (HR 1.20, 95% CI 0.87 – 1.65) and multivariate-adjusted HR (1.39, 95% CI 0.98 – 1.96). There was also no difference in the time to initiation of immunomodulator therapy (HR 1.45, 95% CI 0.82 – 2.57) or anti-TNF therapy (HR 1.11, 95% CI 0.44 – 2.77) among women who were non-users at the time of the index pregnancy (**Figure 1**). In subgroup analysis, mode of delivery did not affect subsequent health outcomes in either CD or UC (p -interaction > 0.05). Similarly, 3% of the vaginal delivery group and 7% of the CS group subsequently required an IBD-related surgery with no statistically significant difference on the propensity score adjusted (HR 0.59, 95% CI 0.19 – 1.84) or multivariate adjusted models (HR 1.75, 95% CI 0.40 – 7.75) (**Figure 2**).

Among 133 CD pregnancies with no prior perianal disease, 2/72 (3%) were noted to have a subsequent diagnosis code for perianal disease compared to 8/61 (13%) in the CS group (unadjusted HR for vaginal delivery compared to CS 0.21, 95% CI 0.04 – 0.99). However, this difference appeared to be due to difference in the selection of mode of delivery based on patient characteristics. Neither the propensity score adjusted model (HR 0.25, 95% CI 0.05 – 1.22) nor multivariate adjusted model (HR 0.19, 95% CI 0.04 – 1.05) demonstrated a difference in subsequent perianal fistula by mode of delivery. Similarly there was no difference in the likelihood of needing subsequent perianal procedures by mode of delivery (**Table 2**).

DISCUSSION

Examination of pregnancy outcomes in patients with CD and UC is an important area of research. Most studies in the field have focused on fertility in such patients, pregnancy and birth outcomes including gestational age and birth weight, and effect of medication exposure during pregnancy, particularly immunosuppressive and anti-TNF medications, on such outcomes^{6-17, 24}. Few have specifically examined the effect of mode of delivery on long-term outcomes in patients with CD and none focusing on UC^{13, 24-27}. Indeed, professional society guidelines and expert opinions only briefly discuss the choice regarding the mode of delivery in IBD patients¹⁰. However, the trend towards growing utilization of CS in both the IBD and general population and tendency towards recommendation of this as preferred strategy due to concern about the impact of perineal and pelvic trauma on disease frequently involving the rectum and lower colon, it is important to provide accurate and objective data regarding the long-term impact of mode of delivery on disease outcomes in those with IBD.

Using data from a large multi-institutional validated electronic medical record cohort of women with either CD or UC, we provide reassuring data that mode of delivery did not impact subsequent disease outcomes in terms of escalation of medical therapy, IBD-related surgery or hospitalization. Importantly, in women with CD who had no prior perianal involvement, there was no increase in risk of a new perianal fistula diagnosis or surgical procedure following vaginal delivery.

There is growing utilization of CS in patients with IBD. More pregnancies occurring after IBD result in a CS than those prior to an IBD diagnosis²². In a meta-analysis by Cornish *et al.*, women with IBD were 1.5 times more likely to delivery via C-section when compared to controls²³. A recent study using an administrative database including data from 2,882 women with CD, identified that between 42.8 – 83.1% of women with CD delivered via C-section²⁴. The reason for this increasing trend is unclear. While perianal disease appears to favor delivery via CS²⁴⁻²⁷, only a small proportion of women with CD have established perianal disease prior to pregnancy. Thus, it is likely that the secular increase in CS may be influenced by patient or provider preferences or obstetric indications. With the wealth of data suggesting that perinatal outcomes are similar in IBD compared to non-IBD patients, it is unlikely that differential distribution of obstetric indications are sole determinants for the high CS rate in those with IBD. Reassuringly, our findings suggest that vaginal delivery is not associated with worse long-term outcomes over a median follow-up of over 4 years in both CD and UC. The potential for complications associated with CS including the higher rate of requiring CS in subsequent pregnancies³⁴, and potential for both short- and long-term post-operative complications suggest that prudence be used in making decisions regarding mode of delivery in patients with IBD. This is particularly relevant as a substantial portion of IBD patients may require abdominal surgery subsequently for management of their disease.

Much of the focus on the effect of perineal trauma has been on the risk of development of perianal complications in those with CD. In patients with established perianal CD, a small study by Ilnyckji *et al.* suggested that women with active disease all reported worsening of perianal symptoms post-partum, while those with inactive disease remained quiescent²⁵. In a study based on survey of gastroenterologists, among those with no history of perianal CD, the rate of perianal complications was greater (17.9%) in those with vaginal delivery leading the authors to speculate that perineal trauma during vaginal delivery may have resulted in subsequent perianal disease²⁷. However, the estimates based on surveys have numerous limitations including lack of objective confirmation of perianal disease and potential for bias in self-report resulting in the high rate of perianal disease reported post-partum. In contrast, Smink *et al.* from the Netherlands identified no increase in risk of progression to perianal involvement in CD patients without perianal disease prior to pregnancy for vaginal compared with CS delivery (5% vs. 14%, p=NS)²⁶. We have recently described that vaginal delivery may be safe in women with perianal disease and not associated with short-term increase in risk of complications, albeit acknowledging a selection bias in women trialing a vaginal birth³⁵. We extend the findings of that study to this larger cohort without perianal disease prior to delivery and provide reassuring data that in a wider population of CD, vaginal delivery does not appear associated with an increase in incidence of perianal or other

complications. However, we could not study whether the patients with active CD were more likely to have perianal complications after vaginal delivery in this EMR dataset. Some of the CS that were performed may have been in women with active CD whose physicians were concerned about the risk for perianal complications.

We readily acknowledge several limitations to our study. First, albeit one of the largest cohort to examine the impact of mode of delivery on subsequent disease outcomes in patients with IBD, our cohort consisted of patients who were seeking care and delivered at one of two major tertiary referral centers in Boston and thus may not be representative of IBD in the community. However as this is indeed the cohort most enriched for severe disease and adverse outcomes, demonstrating the safety of vaginal delivery in this cohort provides reassurance to most women with IBD. Second, this cohort was not adequately powered to examine specifically the effect of mode of delivery on women with established perianal CD. However a complementary study recently published by our group supports the safety of vaginal delivery in that cohort as well, albeit acknowledging a selection bias in the choice of mode of delivery³⁵. Third, we did not have information on the indication for CS (obstetric, provider, or patient preference) or occurrence of complications such as need for episiotomy or perianal tear during vaginal delivery and post-operative complications in the CS group. Fourth, it is possible that we may have inadequate follow-up on patients after delivery to determine IBD outcomes. However, we would not expect this to be differential by mode of childbirth.

In conclusion, we demonstrate that there is no difference in long-term outcomes between women with either CD or UC delivering via vaginal birth compared to caesarean section. Reassuringly, we did not identify an effect of mode of delivery on risk of new perianal disease in women with CD. Further prospective studies examining impact of mode of delivery on functional outcomes such as incontinence would provide complementary data. At this time, patients and providers may be reassured about a trial of vaginal birth for most IBD patients without an obstetric indication for CS delivery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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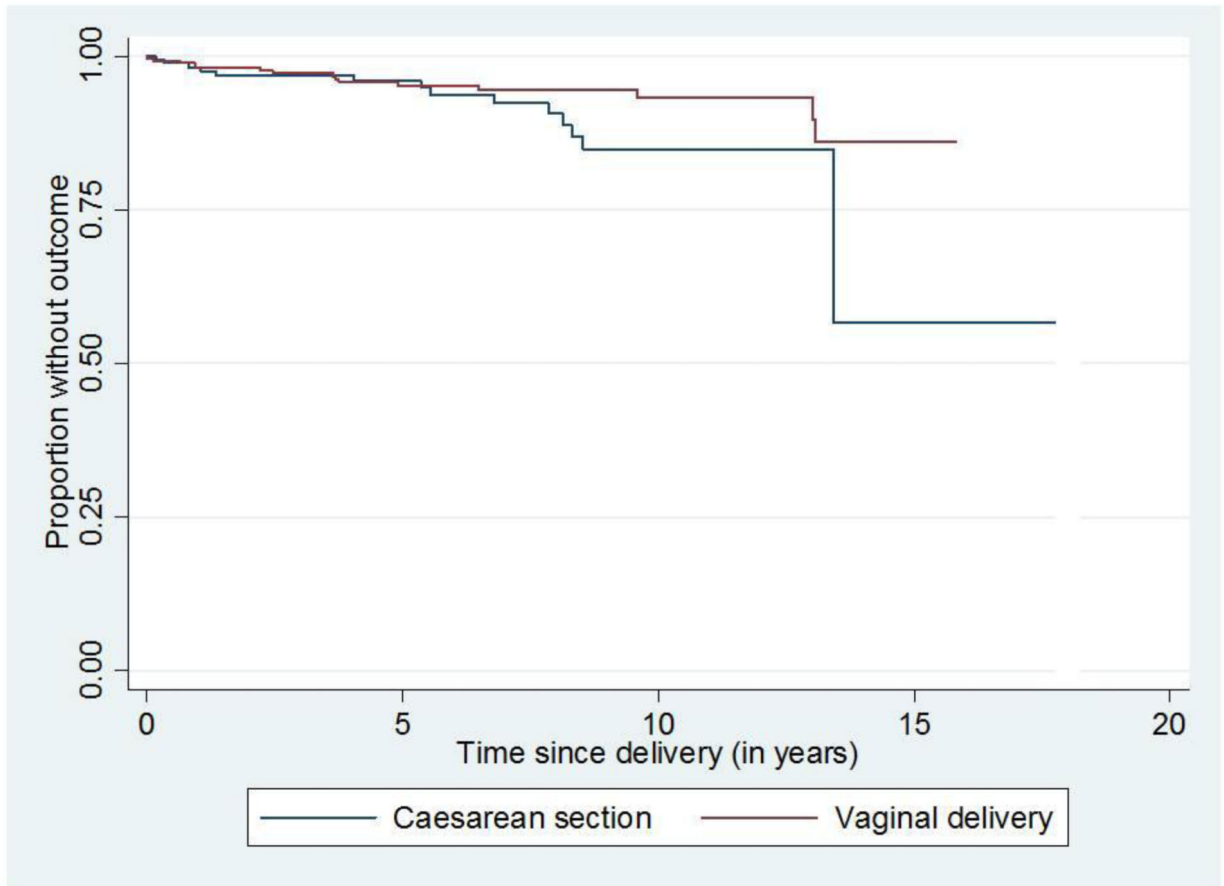
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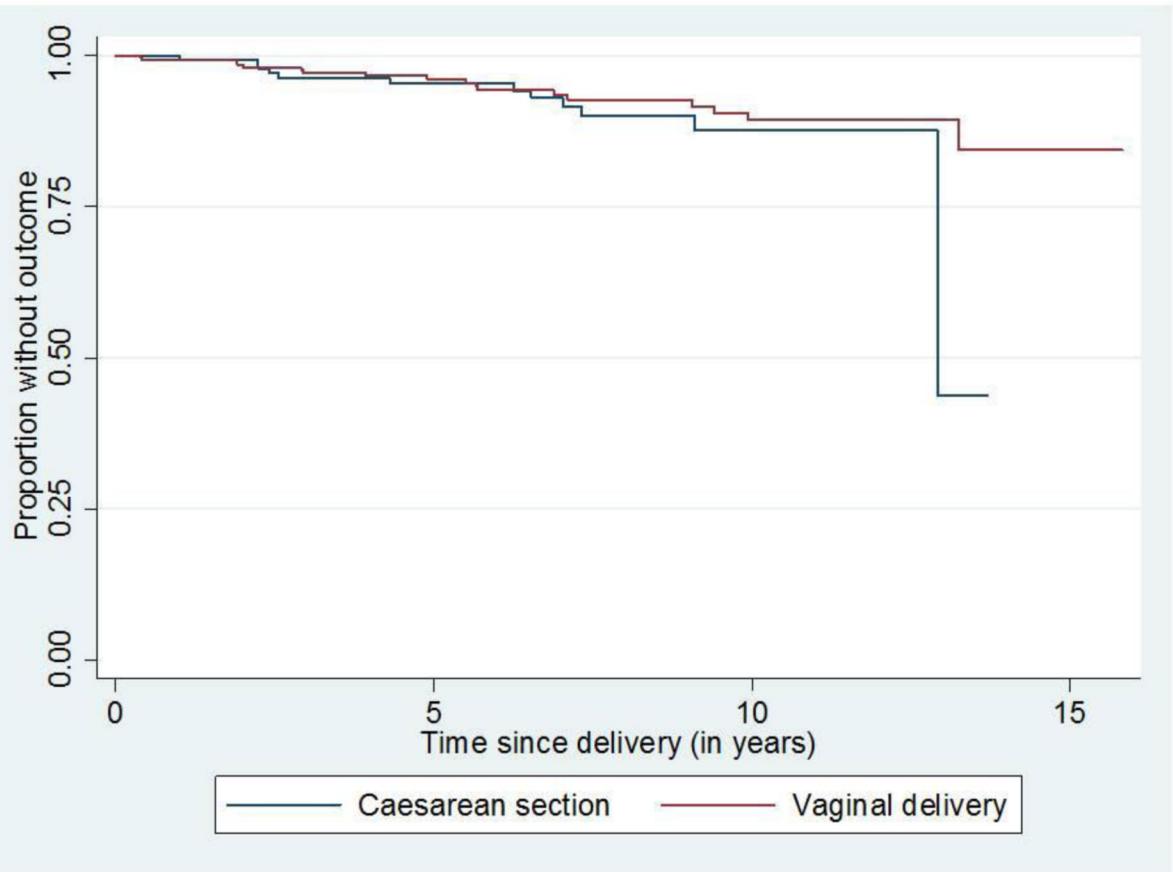


Figure 1. New prescriptions for immunomodulator or anti-TNF biologic therapy, by mode of childbirth



Figure 2.
Risk of IBD-related surgery, by mode of childbirth

Table 1

Characteristics of women with IBD, stratified by modality of childbirth

Characteristic	C-Section (n = 161) %	Vaginal delivery (n = 198) %	p-value
Mean age (in years) (SD)	33.5 (4.9)	32.1 (5.2)	0.01
Mean disease duration at pregnancy (in years) (SD)	3.3 (3.4)	2.9 (2.9)	0.20
Mean age at first IBD code (in years) (SD)	30.1 (5.6)	29.5 (6.5)	0.30
Race			0.43
White	85	88	
Non-white	15	12	
IBD type			0.13
Crohn's disease	47	39	
Ulcerative colitis	53	61	
Perianal disease ⁺	20	8	0.03
Complicated disease behavior ⁺	21	5	0.003
Disease history prior to pregnancy			
Immunosuppression use	19	15	0.30
IBD-related hospitalization	22	17	0.21
IBD-related surgery	9	4	0.02
Duration of follow-up after delivery (in years)	4.9 (3.8)	5.2 (3.9)	0.50

C-section – Caesarean section; SD – standard deviation; IBD – inflammatory bowel disease

Immunomodulators including azathioprine, 6-mercaptopurine, or methotrexate Anti-TNF agents including infliximab, adalimumab, or certolizumab pegol

⁺ - among those with Crohn's disease

Table 2

Multivariate analysis of perianal fistula, IBD-related surgery and hospitalization by delivery type

Outcome	Unadjusted HR (95% CI)	Propensity score adjusted HR (95% CI)	Multivariate adjusted HR [†] (95% CI)
Perianal fistula [‡]	0.21 (0.04 – 0.99)	0.25 (0.05 – 1.22)	0.19 (0.04 – 1.05)
Perianal fistula surgery [‡]	0.33 (0.03 – 3.17)	0.43 (0.04 – 4.20)	0.92 (0.02 – 4.79)
IBD-related hospitalization	1.20 (0.87 – 1.64)	1.20 (0.87 – 1.65)	1.39 (0.98 – 1.96)
IBD-related surgery	0.34 (0.12 – 0.99)	0.59 (0.19 – 1.84)	1.75 (0.40 – 7.75)
Immunomodulator use	1.40 (0.81 – 2.40)	1.31 (0.76 – 2.27)	1.45 (0.82 – 2.57)
Anti-TNF use	0.85 (0.37 – 1.98)	0.93 (0.40 – 2.21)	1.11 (0.44 – 2.77)

Hazard ratios are for comparison between vaginal delivery and C-section (reference category)

HR – Hazard ratio, CI – confidence interval; IBD – inflammatory bowel disease; TNF – tumor necrosis factor α

Immunomodulators including azathioprine, 6-mercaptopurine, or methotrexate Anti-TNF agents including infliximab, adalimumab, or certolizumab pegol

[‡] Among those with Crohn's disease[†] Adjusted for age, disease phenotype, need for surgery, immunosuppression or hospitalization prior to pregnancy, and disease duration