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Pregnancy outcomes in inflammatory bowel disease: Data from a large cohort survey

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Objectives: Inflammatory bowel disease (IBD) can affect young and reproductively active patients. Our aim was to analyze pregnancy outcomes in a large cohort of women with IBD.

Methods: All women with at least one pregnancy were given a questionnaire regarding the outcome of their pregnancy. They were divided into IBD pregnancies and controls depending on whether pregnancy occurred within or over 10 years prior to the diagnosis of IBD.

Results: Three hundred questionnaires were analyzed for a total of 478 pregnancies that led to live-born babies. Age at conception was older in IBD women than in the controls. Active smoking was more frequent in the control group. The risk of intrauterine growth restriction (IUGR) was higher in IBD pregnancies (odds ratio [OR] 3.028, 95% confidence interval [CI] 1.245–7.370, $P = 0.013$). The week of gestation at delivery was lower in the IBD population. And the risk of cesarean section was higher in IBD pregnancies (OR 1.963, 95% CI 1.274–3.028, $P = 0.002$). Among women with IBD pregnancy, the risk of preterm birth was higher in patients with active disease at the time of conception (OR 4.088, 95% CI 1.112–15.025, $P = 0.030$), but lower in patients who continued regular therapy during pregnancy. Similarly, the risk of urgent cesarean section was reduced in the case of disease remission, while the risk of a planned cesarean delivery was higher in patients with perianal disease (OR 11.314, 95% CI 3.550–36.058, $P < 0.01$).

Conclusions: Our study shows a higher risk of IUGR, cesarean section, and poor blood pressure control in IBD pregnancies. We emphasize the importance of achieving disease remission before considering pregnancy.

KEYWORDS
cesarean section, delivery, inflammatory bowel diseases, intrauterine growth restriction, pregnancy

1 | INTRODUCTION

Inflammatory bowel disease (IBD) is a group of chronic, relapsing–remitting diseases of the gastrointestinal tract, mainly including ulcerative colitis (UC) and Crohn's disease (CD).[1,2] At the turn of the 21st century, IBD had become a global disease. Women may be diagnosed with IBD while still fertile;[3,4] therefore, adequate education and counseling are urgently needed for these patients. Although quiescent IBD is not usually associated with decreased fertility,[5] patients with IBD have fewer children than the general population, mostly because of voluntary nulliparity.[6–8] Women with IBD mainly fear the effects of medications rather than the direct consequences of the disease.[9,10] Nevertheless, patients with active IBD have a higher risk of spontaneous abortion, intrauterine growth restriction (IUGR), preterm birth, low birth weight, delivery complications, and of giving birth to small for gestational age (SGA) infants compared with age-matched controls.[11,12] Furthermore, the risk of cesarean delivery is increased in women with IBD, regardless of disease activity.[13,14] Hence, pregnancy in women with IBD should not be discouraged, but needs to be carefully planned and monitored.

To date, data regarding pregnancy in IBD patients are collected from national registries. In this study, we aimed to evaluate the outcomes of pregnancy in outpatients followed at our tertiary IBD Referral Centre to compare the pregnancy outcomes between women with IBD and non-IBD controls, and to evaluate the influence of disease- and drug-related factors on pregnancy outcomes.

2 | PATIENTS AND METHODS

2.1 | Patient enrollment

This was a retrospective, observational, case–control study conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Female patients with IBD who were referred to our IBD Referral Centre (Careggi University Hospital, Florence, Italy) between June and December 2021 and had at least one pregnancy in their medical history, either completed or interrupted, were recruited. Each woman was given a questionnaire regarding the progress and outcome of their pregnancies, upon signature of a written informed consent. We matched the information obtained from the questionnaires to data collected from patients' medical records. Patients aged less than 18 years or those with inability to sign a written informed consent were excluded from the study. All patients who were referred to our centre signed a generic informed consent, which allowed us to anonymously access their personal file for scientific research purposes.

2.2 | Questionnaire

A hardcopy questionnaire was given to each woman with at least one pregnancy in their medical history. The information that was obtained from patients through the questionnaire is reported in Appendix A. The treating physician helped the patients in filling the questionnaire, especially for the questions regarding the complications related to pregnancy and delivery. In case of multiple pregnancies, patients filled different questionnaire for each pregnancy. For each of their pregnancies in IBD, the following data were collected: (a) ongoing therapy at the time of conception and treatment interruption or continuation during pregnancy; (b) clinical disease activity at the time of conception, evaluated with the partial Mayo score (PMS) for UC and Harvey–Bradshaw Index (HBI) for CD;[15,16] and (c) disease flares during the pregnancy. Whether the patient had relied on assisted procreation or not, occurrence of gestational diabetes and/or hypertension was also recorded. Gestational diabetes and hypertension were confirmed according to specific guidelines.[17,18] For each pregnancy, week of gestation at delivery (preterm birth was defined if gestation was <37 weeks),[19] occurrence of IUGR, need for induction of labor, mode of delivery (vaginal or cesarean section), birth weight (low birth weight was defined as <2500 g),[20] and occurrence of placental disease or congenital malformation was collected and recorded. IUGR was defined as the rate of fetal growth below normal in light of the growth potential of a specific infant as per the race and sexes of the fetus.[21]

2.3 | Clinical characteristics of the patients

For each woman we obtained demographic and clinical data, including age at diagnosis, disease duration, smoking, medication history, baseline disease extension based on the Montreal classification,[22] extra-intestinal manifestations (EIMs), and surgery. EIMs included ankylosing spondylitis, sacroiliitis, peripheral arthritis, iritis/uveitis, primary sclerosing cholangitis (PSC), erythema nodosum, and pyoderma gangrenosum.

We evaluated each pregnancy considering all the abovementioned factors at the time of conception. Pregnancies ending in miscarriage in the first trimester (<12 weeks) and intrauterine deaths after the 12th week were excluded. All pregnancies that occurred within 10 years prior to the diagnosis of IBD were included in the IBD group. While those occurred over 10 years before the diagnosis of IBD were considered as the controls. Although genetic factors contributing to disease susceptibility have been described in IBD,[23] it is not a genetic disease. Environmental and immunological factors also contribute to disease development. In support of our method, previous studies have underlined that diagnostic delay in IBD, although greater in CD than in UC, is generally inferior to 4 years in large cohorts.[24–28] For this reason, women who become pregnant more than 10 years before the diagnosis of IBD are unlikely to be undiagnosed patients and pregnancies that occurred before the 10-year cut-off can be considered as not influenced by the intestinal disease.

2.4 | Statistical analysis

All the statistical analyses were performed using SPSS Statistics version 26.0 (IBM, Armonk, NY, USA). The Shapiro–Wilk test was used

to assess the normality of distribution of the variables. All the continuous variables were non-normally distributed and are expressed as median and interquartile range (IQR), while categorical variables are presented as numbers and percentages or frequencies. Descriptive statistics were used to compare the characteristics of the two groups of pregnancies. Continuous variables were compared using the Mann–Whitney *U*-test, while categorical variables were compared with a Yate's χ^2 test or a Fisher's exact test (depending on the sample size). The coefficient Cramer's V was calculated to measure the strength of the association. Odds ratio (OR) was used to compare the relative odds of the occurrence of various outcomes in our population. A two-sided *P* value of less than 0.05 was considered statistically significant.

3 | RESULTS

A total of 1099 patients were enrolled, of whom 300 agreed to answer the questionnaire (27.3% response rate: 129 [43.0%] had CD and 171 [57.0%] had UC). Baseline and demographic characteristics of the patients are shown in Table 1, while a flowchart explaining the entire inclusion process is shown in Figure 1.

Out of 575 pregnancies, 90 (15.7%) ended in miscarriage before the 12th week. For this reason, we included in the study the remaining 485 pregnancies, which were divided into 187 (38.6%) IBD pregnancies and 298 (61.4%) controls.

We observed seven (1.4%) cases of intrauterine death, of which two (1.1%) were in the IBD pregnancy group and five (1.7%) in the control group, with no statistically significant difference ($P = 0.710$). The number of pregnancies with live-born babies were 478, of which there were 185 IBD pregnancy cases and 293 controls. Women with IBD were significantly older than the controls (33 y [IQR 29–37 y] vs 27 y [IQR 23–31 y], $P = 0.001$). The proportion of patients with an exposure to cigarette smoke during pregnancy was significantly lower in women with IBD than in the control group (10.8% vs 18.8%, $P = 0.019$). IBD patients had a higher risk of poor blood pressure control during pregnancy compared to the controls (5.9% vs 2.0%, $P = 0.011$). The risk of IUGR was found to be higher in the group of IBD pregnancy women than in the controls (OR 3.028, 95% confidence interval [CI] 1.245–7.370, $P = 0.013$). Median birth weight of the infants was similar between the two groups (3200 g [IQR 2900–3250 g] in the IBD pregnancy group vs 3300 g [IQR 3000–3650 g] in the control group, $P = 0.060$). The time of gestation at delivery was short in the IBD pregnancy group (39 wks [IQR 38–40 wks] vs 40 wks [IQR 38–40 wks], $P = 0.002$); however, we did not find any statistically significant difference in preterm birth rates between the two groups ($P = 0.450$). Women with IBD underwent cesarean section more frequently than controls (OR 1.963, 95% CI 1.274–3.028, $P = 0.002$). In women with IBD pregnancy, eight (4.3%) pregnancies ended with an urgent cesarean delivery due to obstetric issues (nuchal cord, meconium-stained amniotic fluid, podalic presentation) or disease complications (bowel occlusion, ileal fistulae). Detailed results are summarized in Tables 2 and 3.

TABLE 1 Demographic characteristics of the population.

Characteristics	All (n = 300)
Disease type (n, %)	
CD	129 (43.0)
UC	171 (57.0)
Age at diagnosis years [median (IQR)]	34 (19-45)
History of smoking at diagnosis (n, %)	
Active smoker	69 (23.0)
Former smoker	31 (10.3)
Never smoker	200 (66.7)
Phenotype (CD, Montreal classification) (n, %)	
A1	10 (7.8)
A2	76 (58.9)
A3	43 (33.3)
L1	41 (31.8)
L2	21 (16.3)
L3	67 (51.9)
L4	13 (10.1)
B1	51 (39.5)
B2	56 (43.4)
B3	22 (17.1)
Bp (perianal disease)	25 (19.4)
Phenotype (UC, Montreal classification) (n, %)	
Age ≤16 years	11 (6.4)
Age 17–40 years	107 (62.6)
Age >40 years	53 (31.0)
E1	27 (15.8)
E2	72 (42.1)
E3	72 (42.1)
History of EIMs (n, %)	56 (18.7)
History of surgery (n, %)	73 (24.3)
History of medications (n, %)	
No medication or mesalamine	179 (59.7)
Anti-TNF-α agent	48 (16.0)
IMS	38 (12.7)
More than 1 previous treatment, either IMS or biological agent, not combined	25 (8.3)
Combined IMS and anti-TNF-α agent	5 (1.7)
Ustekinumab	4 (1.3)
Vedolizumab	1 (0.3)

Abbreviations: CD, Crohn's disease; EIM, extra-intestinal manifestation; IMS, immunosuppressants; IQR, interquartile range; TNF-α, tumor necrosis factor α; UC, ulcerative colitis.

The majority (151/185 [81.6%]) of IBD pregnancies were carried out without interruption or modification of ongoing medical therapy. In 173 (93.5%) out of the 185 IBD pregnancies, the patients had a quiescent disease at conception. A disease flare occurred in 23 (13.3%) of the 173 cases. In the 12 cases in which the disease was clinically active at conception, it remained active for the entire duration of gestation.

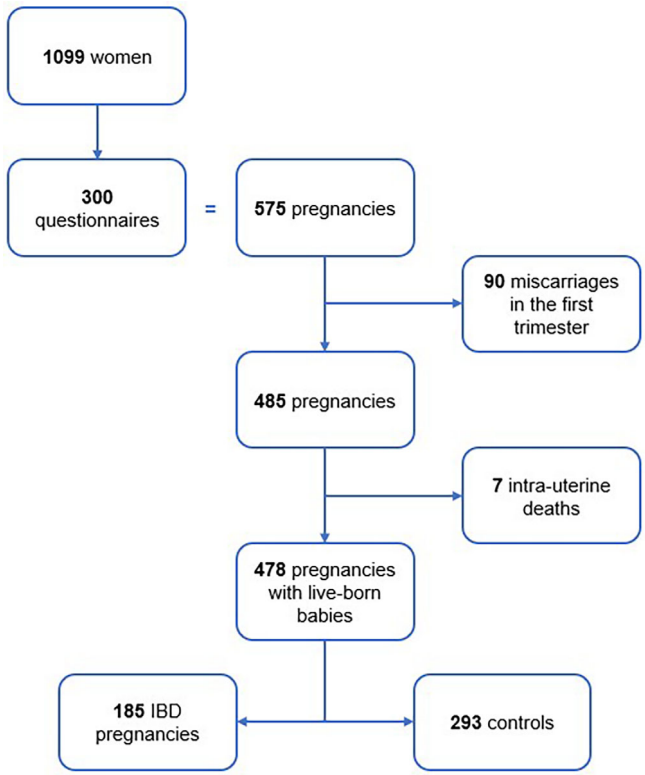

FIGURE 1 Flowchart of patient enrollment. Abbreviation: IBD, inflammatory bowel disease

Preterm delivery occurred in 21 (11.4%) in the IBD group. Compliant patients had a lower risk of preterm delivery ($P = 0.040$). This risk was significantly higher in patients with active disease at the time of conception (OR 4.088, 95% CI 1.112–15.025, $P = 0.030$). Similarly, the risk of urgent cesarean section was reduced in case of disease remission ($P = 0.020$), while the risk of an elective cesarean section was higher in patients with perianal disease (OR 11.314, 95% CI 3.550–36.058, $P < 0.01$).

4 | DISCUSSION

IBD is often diagnosed in women of childbearing age. High rates of voluntary nulliparity in these patients unveil the need for better counseling and support.[4] Pregnancy is a very important and extremely delicate event in a woman's life. Among women with IBD, pregnancy carries an increased risk of complications and cesarean delivery, although risks can be effectively reduced with adequate treatment of the intestinal disease.[5,12,13] For this reason, pregnancy should not be discouraged by physicians, but needs to be carefully planned and monitored. In the current study we compared pregnancy outcomes before and after IBD diagnosis, and investigated the association between pregnancy outcomes and disease- and medication-related factors. Women with IBD who become pregnant during a quiescent phase of the disease are known to have the same risk of exacerbation as nonpregnant women, while women who begin their pregnancy with active disease are at a risk of maintaining disease activity during gestation.[29,30] As the purpose of our research was to evaluate the effects of IBD on pregnancy outcomes, we did not assess the impact of pregnancy on IBD activity.

Given the difficulty of collecting data on spontaneous abortions and intrauterine deaths in a retrospective manner, we excluded them from our discussion. However, the percentage of spontaneous first-trimester miscarriages in our population did not differ from that in the general population,[31] and the rates of intrauterine deaths were similar in women with IBD pregnancy and the controls ($P = 0.710$). In a recent meta-analysis, Kim et al demonstrated that disease activity during the periconception period was associated with an increased risk of first-trimester miscarriages and intrauterine deaths.[14] In our cohort, most women had a quiescent disease at the time of conception, which supports the absence of statistically significant differences between the two groups in terms of intrauterine deaths.

In our patient cohort, women with IBD were about 6 years older than controls at the time of conception ($P = 0.001$). This is in line with a previous study.[32] As discussed above, we believe women with IBD avoid or delay pregnancy out of fear or postpone having children in case of scarce disease control, while waiting for disease remission. Previous studies have also shown that sexual disfunction and dyspareunia are more frequent in women with IBD than in controls.[33–35] In addition, women with IBD are more likely to have a poor body image, especially those who have undergone surgery.[36]

As previously reported in the literature, we found lower rates of maternal smoking in the IBD group compared to controls ($P = 0.019$). In the control group, the prevalence of smoking was similar to that reported in Italy in 2015–2016.[37] These findings might be explained by the increased medical attention and counseling that IBD patients receive during pregnancy compared to low-risk pregnancies.[32,38]

In our study, IBD patients had a higher risk of poor blood pressure control than non-IBD patients ($P = 0.011$). The only known risk factor for maternal hypertension in patients with IBD is the use of systemic steroids or cyclosporine.[39,40] As hypertension was not associated with systemic steroids or cyclosporine use in our cohort, our results could be explained by older age at pregnancy in IBD women.[41] Only two patients experienced a major hypertensive complication such as pre-eclampsia or eclampsia. In both cases, there were no other complications and pregnancy ended with elective cesarean delivery.

The IBD group had a higher prevalence of IUGR than the control group ($P = 0.013$). Few studies have evaluated the risk of IUGR in pregnant women with IBD. Bengtson et al reported a higher risk of IUGR related to an inadequate gestational weight gain (OR 1.51, 95% CI 0.64–3.52),[42] while Lee et al found an increased risk of IUGR in patients with CD than the controls (OR 2.89, 95% CI 1.59–5.26).[43] In our study, a higher risk of IUGR was not associated with low birth weight of the infants, and this is in line with the current literature.[44] Several studies have reported that IBD women are more likely to deliver low-birth-weight babies, although we found similar rates in both study groups.[14,45]

The week of gestation at delivery was lower in the IBD population (39 wks [IQR 38–40 wks] vs 40 wks [IQR 38–40 wks],

TABLE 2 Outcomes in pregnancies with live-born babies

	Total (n = 478)	IBD (n = 185)	Controls (n = 293)	*P* value
Age at conception, years (median [IQR])	30 (25–34)	33 (29–37)	27 (23–31)	**0.001**
Active smoking (n, %)	75 (15.7)	20 (10.8)	55 (18.8)	**0.019**
Assisted procreation (n, %)	14 (2.9)	8 (4.3)	6 (2.0)	0.164
Sex of the infants (n, %)				0.280
Male	255 (53.3)	93 (50.3)	162 (55.3)	
Female	223 (46.7)	92 (49.7)	131 (44.7)	
Median birth weight of the infants, g (median [IQR])	3280 (3000–3600)	3200 (2900–3250)	3300 (3000–3650)	0.060
Median time of gestation at delivery, weeks (median [IQR])	40 (38–40)	39 (38–40)	40 (38–40)	**0.002**
Gestational diabetes (n, %)	25 (5.2)	15 (8.1)	10 (3.4)	0.060
Gestational hypertension (n, %)	17 (3.6)	11 (5.9)	6 (2.0)	**0.011**
Preterm delivery (<37 weeks) (n, %)	48 (10.0)	21 (11.4)	27 (9.2)	0.450
Cesarean section (n, %)	109 (22.8)	55 (29.7)	54 (18.4)	**0.002**
Induction of labor (n, %)	101 (21.1)	41 (22.2)	60 (20.5)	0.564
Delivery complications (n, %)	40 (8.4)	17 (9.2)	23 (7.8)	0.610
PPROM	2 (0.4)	1 (0.5)	1 (0.3)	
Intrapartum bleeding	4 (0.8)	2 (1.1)	2 (0.7)	
Oligohydramnios	2 (0.4)	1 (0.5)	1 (0.3)	
Retained placenta	4 (0.8)	1 (0.5)	3 (1.0)	
Post-partum bleeding	4 (0.8)	3 (1.6)	1 (0.3)	
Meconium-stained amniotic fluid	2 (0.4)	0 (0)	2 (0.7)	
Shoulder dystocia	11 (2.3)	4 (2.2)	7 (2.4)	
Cord issues	3 (0.6)	0 (0)	3 (1.0)	
Use of forceps	4 (0.8)	1 (0.5)	3 (1.0)	
Fetal suffering	1 (0.2)	1 (0.5)	0 (0)	
Bowel fistulae	2 (0.4)	2 (1.1)	0 (0)	
Bowel occlusion	1 (0.2)	1 (0.5)	0 (0)	
IUGR (n, %)	22 (4.6)	14 (7.6)	8 (2.7)	**0.013**
Congenital abnormalities (n, %)	3 (0.6)	2 (1.1)	1 (0.3)	0.379
Trigonocephaly	1 (0.2)	1 (0.5)	0 (0)	
Heart abnormalities	1 (0.2)	1 (0.5)	0 (0)	
Brain swelling	1 (0.2)	0 (0)	1 (0.3)	
Placental disease (n, %)	14 (2.9)	7 (3.8)	7 (2.4)	0.895
Placental abruption	12 (2.5)	6 (3.2)	6 (2.0)	
Placenta previa	2 (0.4)	1 (0.5)	1 (0.3)	

Bold characters represent statistical significance. Abbreviations: IBD, inflammatory bowel disease; IQR, interquartile range; IUGR, intrauterine grow restriction; PPROM, preterm premature rupture of membranes.

$P = 0.002$), especially in cases of active disease at conception ($P = 0.030$); however, we did not find any difference in preterm birth rates between the two groups ($P = 0.450$). Our results confirm the recent findings of the retrospective study of a Chilean cohort, in which the authors found an association between disease flares and preterm births.[46] Our study population, however, is much larger.

Our data concerning cesarean delivery (more frequent in the IBD group irrespective of CD or UC; $P = 0.002$) reflects what is already known.[12,14,45,47] Cesarean section was reported to be more frequent in patients with CD, but not with UC.[48] A large European study demonstrated that older age at delivery and therapy interruption were risk factors for cesarean delivery in pregnant women with UC.[49] In our IBD cohort, women with CD and perianal disease were more likely to undergo a cesarean section. In a large retrospective study on 2882 pregnant women with CD, with or without perianal disease, perianal disease was independently associated with fourth-grade perianal lacerations (OR 10.9, 95% CI 8.3–14.1, $P < 0.001$).[50] We did not observe any case of severe perianal laceration in our patients who underwent vaginal delivery. In any case, current guidelines agree on suggesting a planned cesarean delivery in case of fistulizing perianal disease and

TABLE 3 Risk comparation between inflammatory bowel disease and controls

	OR	95% CI	*P* value
Gestational diabetes	2.180	0.967–4.912	0.060
Preterm delivery	1.261	0.691–2.305	0.450
Cesarean section	**1.963**	**1.274–3.028**	**0.002**
Induction of labor	1.157	0.739–1.812	0.564
IUGR	**3.028**	**1.245–7.370**	**0.013**
Placental disease	0.909	0.300–2.756	0.895

Bold characters represent statistical significance. Abbreviations: CI, confidence interval; IUGR, intrauterine grow restriction; OR, odds ratio.

previous colectomy with ileal pouch-anal anastomosis (IPAA) to reduce postpartum sphincter or pelvic floor impairments.[4,38,51]

Finally, our data confirm the present literature for what concerns the use of medications for IBD during pregnancy. We found no association between the use of any medication and pregnancy complications. As pointed out by various authors, most therapies should be continued throughout pregnancy to maintain disease remission. In fact, most drugs used to treat IBD do not have negative effects on gestation; conversely, a relapse of the disease can lead to poor pregnancy outcomes.[4,52,53] An extensive discussion about the safety of IBD medications in pregnancy eludes the purposes of our research.

The main limitation of our study was the lack of a control arm outside the IBD population. However, women who became pregnant at least 10 years prior to the diagnosis of IBD are unlikely to be undiagnosed cases and can therefore be considered as the controls. Our methodology implicates that women from the IBD cohort are older than those from the control group. This can generate a bias, since the risk of pregnancy complications, including poor blood pressure control, increases with womens' age.[54] However, the median age of our IBD cohort is still under 35 years, which is considered the age from which the risk rapidly increases.[55,56] Another limitation could be the fact that in the questionnaire we provided, patients could not specify when spontaneous first-trimester miscarriages had occurred (before or after the IBD diagnosis); however, the rate of spontaneous first-trimester abortions we found in our population is equal to that of the general population, allowing us to exclude these pregnancies from the analysis without creating a bias. We also did not have data regarding singleton or twin pregnancies in our cohort, as this information was not included in the questionnaire. However, there are no significant literature reports on any specific risk of conducting a twin pregnancy for IBD patients. Finally, our research is limited by the disadvantages of the use of self-reported outcomes and a retrospective design, including the fact that we could not actively interfere at planned endpoints to evaluate predetermined outcomes. Anyhow, the thoroughness with which the patients answered the questionnaire and our detailed electronic records enabled us to have enough data to carry out reliable statistical analyses.

In conclusion, IBD pregnancies were at higher risk of IUGR, shorter time of gestation, and cesarean delivery compared to the controls. No differences between the two groups were found in terms of congenital malformations and other major delivery complications. Furthermore, in IBD patients poor pregnancy outcomes were associated with active disease at the time of conception and during gestation.

Our findings are in line with previous studies that vaginal delivery should be allowed in most women with IBD. Patients with quiescent perianal disease or an IPAA should consider undergoing an elective cesarean section, whereas a planned cesarean delivery is indicated in women with active perianal disease. We would like to emphasize the importance of adequate multidisciplinary preconceptional counseling, as patients and physicians should share the objective of achieving disease remission before conception in order to improve pregnancy outcomes.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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APPENDIX A: Questionnaire

1. Demographic data (name, date of birth)
2. Disease (ulcerative colitis or Crohn's disease)
3. Year of diagnosis
4. Year of pregnancy
5. First/second/third/… pregnancy
6. Assisted reproduction (yes/no)
7. Smoking habit during pregnancy (active smoker/non-smoker)
8. Newborn sex (male/female)
9. Newborn weight (grams)
10. Week of gestation at delivery (number)
11. Delivery mode (natural/cesarean section)
12. Delivery complications (yes/no; in case of yes, free text to specify)
13. Induction of labor (yes/no)
14. Placental disease (no/placental abruption/placenta previa/other—free text to specify)
15. Hypertensive disorders in pregnancy (no/chronic hypertension/pre-eclampsia/eclampsia/gestational hypertension/other—free text to specify)
16. Gestational diabetes (yes/no)
17. Miscarriage (yes/no)