Pregnancy with inflammatory bowel disease: Outcomes for mothers and their children at a European tertiary care center

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Abstract

Aim: The study aimed at investigating pregnancy complications, birth outcomes, and postnatal child development in pregnancies of women with inflammatory bowel diseases (IBDs).

Methods: This is an uncontrolled retrospective single-center study between 2014 and 2019. It is a mixed-method cross-sectional study using data from (1) electronic patient records and (2) questionnaires and copies of mothers’ and children’s health booklets. Disease activity and IBD medications were analyzed and related to pregnancy complications, birth outcomes, and postnatal child development using mixed models for statistical analyses.

Results: Fifty live births from 46 patients were included. Disease activity anytime during pregnancy occurred in 56%. Biologics were applied in ca. 25% of pregnancies, mostly only through the second trimester. Pregnancies of mothers with active disease were slightly shorter than those of mothers with inactive disease (37.4 weeks vs. 38.9 weeks). Adverse pregnancy outcomes were reported in 28% of the live births, including small for gestational age in 6%, low birth weight in 18%, and preterm birth in 20%. Postnatal developmental abnormalities and health problems were reported in 26.8% of the children. Mixed model analyses failed to reveal significant associations between IBD activity and IBD medications during pregnancy and pregnancy complications, perinatal birth outcomes, and postnatal child development.

Conclusion: Despite a tendency of shorter pregnancies in patients with active IBD and lower birth weight and birth size in patients with IBD-related therapy during pregnancy, disease activity and medications did not significantly influence pregnancy, birth, and developmental outcomes.

Key words: child development, complications, Crohn’s disease, inflammatory bowel disease, outcome, pregnancy, ulcerative colitis.

Introduction

The condition of inflammatory bowel diseases (IBDs) includes Crohn’s disease (CD), ulcerative colitis (UC), and IBD unclassified (IBDU). IBDs are complex, poorly understood, incurable inflammatory diseases of the gastrointestinal tract with mostly relapsing or chronic disease courses. At present, more than one million residents of the United States and 2.5 million residents of Europe are estimated to suffer from IBD.

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IBDs often affect patients of reproductive age. In spite of an increasing body of evidence showing that the majority of IBD-related medications can be maintained during pregnancy and breastfeeding, and in spite of international guidelines recommending remission as the pre-eminent goal throughout pregnancy, considerable fears and uncertainties are likely to influence both the patients’ and the treating physicians’ decisions concerning IBD-focused drug therapy during pregnancy.

Disease activity at the time of conception seems to be an important factor in the further course of IBD during pregnancy. On average, one in three patients who are in remission in the beginning of their pregnancy will develop a disease flare during the further course of pregnancy. If conception takes place during an IBD flare, the risk of further flares during pregnancy increases for both CD and UC patients. Therefore, remission should always be a primary therapy goal prior to conception for women with IBD.

Women with IBD appear to have a higher risk of pregnancy complications compared to the general population. Several studies have analyzed the impact of IBD on birth outcomes. According to their results, preterm deliveries, small for gestational age (SGA), low birth weight, and spontaneous abortions (stillbirths) occurred more frequently in IBD patients than in the general population. Studies relating disease activity during pregnancy to birth outcomes show that active disease and disease severity are associated with worse birth outcomes in IBD patients. In contrast, the use of IBD-related medications during pregnancy seems to carry no excess risk for pregnancy complications except for methotrexate. Less data are available on long-term outcomes of children who were born to women with IBD. A study published in 2016 which investigated whether offspring of women suffering from IBD during their pregnancies were at increased risk for long-term pediatric morbidity revealed no detrimental effect of maternal IBD on child health.

The goal of the present study was to assess the impact of IBD and related medications on pregnancy complications, birth outcomes, and child development.

**Study objectives**
The primary study objectives were to describe birth outcomes and postnatal health and the development of the children who were born to the included mothers suffering from IBD during their pregnancies. Secondary study objectives were to analyze for potential associations between birth outcomes and child health and development on the one hand and IBD activity as well as IBD therapies on the other hand. Further secondary study objectives were to record the occurrence of pregnancy complications in relation to disease activity and to IBD-related medications during pregnancy.

**Patients and Methods**

**Study design**
The study is a single-center mixed-method retrospective cohort study. To achieve a comprehensive picture, information was retrieved from four different, complementary data sources: (1) electronic patient records of the included pregnant women at the IBD outpatient clinic of the Heidelberg university hospital, (2) individually designed paper-based questionnaires filled in retrospectively by the mothers, (3) health booklets for pregnancy monitoring, and (4) health booklets for child developmental monitoring. Thereafter, the data collected from these different sources were merged and analyzed.

**Ethical considerations**
For the first part of the study—containing only retrospective analyses of data from the electronic patient records—the necessity to obtain informed consents from all patients was waived by the local Ethics Committee based on § 13 Abs. 1 LDSG BW (federal state law of Baden-Wuerttemberg, Germany). For the second part of the study, which was based on patient questionnaires, all participants had to sign an informed consent form. The study was approved by the local Ethics Committee (Alte Glockengiesserei 11/1, 69115 Heidelberg, Germany; protocol number: S-820/2018).

**Inclusion and exclusion criteria**
Inclusion criteria of the present study were: (1) pregnancies documented in the electronic patient records of the IBD outpatient clinic of Heidelberg university hospital since January 1, 2014; and (2) ascertained diagnosis of any IBD—comprising CD, UC, and IBDU according to ECCO criteria. Exclusion criteria were: (1) spontaneous abortion (stillbirth); (2) incomplete information on pregnancy outcome and child development; and (3) pregnancies...
ending after June 1, 2019, representing the cutoff time point for data acquisition.

Data acquisition from electronic patient records
Initially, the names of all eligible female patients were identified from a systematically maintained IBD registry established at the IBD outpatient clinic of Heidelberg university hospital. Using the resulting list, the data of interest were retrieved from fully electronic patient charts: these were mostly generated by the physicians of the IBD outpatient clinic, but—if available—also from other departments of the hospital, such as the gynecology and obstetrics department. Another method of data acquisition was via an electronic data archive providing scanned medical reports from external clinics and practices. Data of interest were: entity of IBD (CD, UC, IBDU), year of first diagnosis of IBD, disease categories according to Montreal classifications for CD or UC,17 prior surgical interventions (separated by abdominal and non-abdominal), presence of an ostomy at start of pregnancy, total number of pregnancies per patient prior to index pregnancy, number of live births per patient until the end of follow-up, position of index pregnancies in relation to prior pregnancies, date of birth, and pregnancy duration in weeks, clinical disease activity in the beginning of pregnancy, any disease activity during pregnancy, presence of fistulae, and IBD medications and their changes during pregnancy (categorized by trimesters).

Data acquisition from questionnaires
Prior to the start of this study, a printed questionnaire in German language was designed. It contained questions about the course of pregnancy, pregnancy complications, time and mode of birth, and the development of the child. In addition, the study participants were asked to include copies of their records of prenatal and natal care as well as of the documentation of baby and child developmental check-up examinations (called “U” examinations in Germany). The patients were called. An informative letter, an informed consent form to be signed, and a questionnaire were mailed to the possible participants. Every letter also contained a prepaid envelope to return the signed informed consent forms, the filled-in questionnaires, and the copies of the screening documents to the study office.

Definitions
Disease activity was scored by the Harvey Bradshaw index (HBI) for CD,18 the Simple Clinical Colitis Activity Index (SCCAI) for UC,19 and either by the HBI or the SCCAI for IBDU (as applied by the treating physician). For CD, active IBD was defined as an HBI score of ≥5, while a SCCAI score of ≥2 indicated active IBD in UC. Disease extent and behavior were categorized using the Montreal classification for CD and UC, respectively.17 The achievement of defined child development milestones was assumed whenever no developmental abnormalities were mentioned in the documentation of regular pediatric examinations, and when normal development was confirmed by the responsible pediatrician. In Germany, nine pediatric screening examinations (U1–U9) are intended until the age of 64 months. At every examination, the children are medically examined and checked for the achievement of certain age-related developmental milestones.

Pregnancy complications were defined as maternal and fetal adverse events during pregnancy. Adverse pregnancy outcomes were defined as any pregnancy outcomes other than normal live births, including—most commonly—preterm delivery and low birth weight. Preterm delivery is defined as any delivery prior to the end of 37 weeks of gestation (i.e., less than 259 days). The international definition of low birth weight is a birth weight of <2500 g. SGA newborns are defined as newborns with a birth weight below the tenth percentile for the gestational age. Birth weights and sizes were determined directly after birth at U1 by the obstetric staff. The data were assumed from the children’s examination booklets.

Statistical analyses
The software R Version 3.6.2 (2019-12-12) was used for statistical analyses.20 Descriptively, nominal data were indicated as ratios and percentages. Continuous data were presented as minimum, maximum, mean, and standard deviation (SD). For further statistical analyses, univariable mixed regression models with woman-specific random intercepts were conducted to account for the multiple pregnancies of some of the women. The analyzed independent variables were included as fixed effects. The R-package lmerTest was used to calculate the mixed regression models.21 The results of the mixed models are shown as OR for binary variables and as mean difference (MD) for continuous variables with their confidence intervals (CIs).
and p-values each. The level of significance was set to $\alpha = 0.05$. All reported CIs are 95% CIs. No corrections for multiple comparisons were performed.

Results

Questionnaire response rate

The details of questionnaire response in this study are depicted in a flow chart (Figure 1). In all, 51 patients were eligible to receive telephone calls. Seven patients never answered the telephone. Three patients were successfully called but opted out of the questionnaire and therefore were not sent study letters. Thus, 48 letters were mailed to the patients (including the seven patients who had never answered the phone). In two cases, the letters were returned by the postal service as undeliverable because mailing addresses of the patients had changed. Three patients who had agreed to take part in the study decided to opt out after...
being reminded to return their questionnaires. Another seven patients did not answer the letters.

In total, 36 patients completed the questionnaires. Taking into account that some patients filled in the documents for more than one child, 40 completed questionnaires, but only 26 copies of medical screening documents for mothers and children were returned.

Included pregnancies

At first, 68 pregnancies of 61 eligible patients were identified. Eight pregnancies in seven patients had to be excluded due to missing documentation of outcomes. Ten pregnancies in eight patients were excluded due to spontaneous abortions. Thus, 50 pregnancies in 46 patients were included according to the inclusion and exclusion criteria described above. Among the 46 included patients, 25 (54.3%) suffered from CD, 16 (34.8%) from UC, and 5 (10.9%) from IBDU. The pregnancies covered 28 pregnancies of CD patients, 16 of UC patients, and 6 of patients suffering from IBDU. They resulted in the patients’ first children in 32 cases (64%), their second children in 14 cases (28%), and their third children in 4 cases (8%). At the end of data acquisition, the children were 2.5 years old (SD: 1.6 years; n = 47).

Baseline characteristics of the included patients and pregnancies

Baseline characteristics of the included patients are presented in Table 1A. At first diagnosis of their IBD, the patients were 22.2 years (SD: 5.9 years) old. The mean disease duration until the start of the index pregnancy was 8.1 years (SD: 5.3 years), while the mean age was 29.8 years (SD: 4.1 years). Nineteen of the 46 included patients (41.3%) had undergone at least one abdominal surgery prior to the observed pregnancies, 9 of the operations being IBD-related bowel surgeries (19.6%). Seven patients (15.2%) had undergone at least one fistula-related surgical intervention prior to the observed pregnancies. Three patients (6.5%) became pregnant with a preexisting stoma.

In Table 1B, baseline characteristics and courses of the included pregnancies are presented. The age at the beginning of pregnancy was 29.8 years (SD: 4.1 years). Disease duration to the beginning of pregnancy was 8.1 years (SD: 5.3 years). Nine patients (18%) had active IBD in the beginning of their pregnancies.

Potential risk factors for pregnancy other than IBD (potential confounders)

All included pregnancies were singleton pregnancies. While six patients (13%) had a history of smoking, none of the patients smoked during pregnancy. Maternal infections were diagnosed in 13 pregnancies (26%). They included Clostridioides difficile-associated colitis (n = 3), upper respiratory infections (n = 3), gastrointestinal infections (n = 2), B Streptococcus infections (n = 2), one herpes virus infection, one influenza infection, one intestinal abscessed, one cystitis, and one unclassified genital infection. The prevalence of maternal infections did not differ significantly between pregnancies under immunosuppressive therapy and without immunosuppressive therapy (OR 1.83; CI 0.52–8.10, p = 0.424).

Disease activity during pregnancy

For nine pregnancies (18%), the presence of active disease was documented at the beginning of pregnancy, while active disease at any time point during pregnancy was noted in 28 cases (56%) (Table 1B). Supplementary Table S1 summarizes the distribution of active disease according to disease entity and pregnancy phase. Considering all included pregnancies of CD patients, the mean HBI score at the beginning of pregnancy was 0.8 (SD: 2.4); for pregnancies of UC patients, the mean SCCAI at the beginning of pregnancy was 0.6 (SD: 1.5). In two pregnancies of CD patients, an actively secreting perianal fistula was documented at the beginning of pregnancy. Active IBD during pregnancy was found in 23 pregnancies (46%). The mean pregnancy duration in remission until start of active IBD was 17.4 weeks (SD: 9.5 weeks). Figure 2 illustrates the probability of developing active disease depending on pregnancy duration.

IBD-related medications during pregnancy

In 37 of the 50 included pregnancies (74%), the patients were under immunosuppressive therapy. Table 1B and especially Supplementary Table S1 provides an overview over the IBD-related medications which the included patients were treated with during their pregnancies. Tumor necrosis factor alpha (TNFα) antagonists were applied in 28% of the pregnancies in the first and second trimester, but only in 4% of the pregnancies in the third trimester. The rates of systemic corticosteroid use were contrary; they were lowest in the first trimester and increased to 34% in the...
third trimester. Three patients were treated with corticosteroids after they had paused anti-TNF-α therapy. Rates of thiopurine intake ranged between 6% and 8%.

Modes of delivery
Among the 50 live births, 24 (48%) were spontaneous births, while 26 children (52%) were delivered via Cesarean section. The indications for Cesarean section deliveries were: request by the mothers (n = 3), recommended by obstetricians due to IBD (n = 3), pelvic presentation of the fetus (n = 2), birth arrest (n = 2), HELLP syndrome (n = 2), intolerable pain (n = 2), premature rupture of membranes (n = 1), severe pre-eclampsia (n = 1), oligohydramnios and fetal growth restriction (n = 1), placenta previa (n = 1), and polyhydramnios (n = 1).

Primary Study Outcomes
Birth weight and size, breastfeeding
The mean birth weight was 2975 g (SD: 818 g; n = 48). Children delivered by Cesarean section weighed

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TABLE 1 Baseline characteristics

A: Baseline characteristics of the 46 included patients at beginning of first evaluated pregnancy in the study

| Patients (n) | CD    | UC    | IBDU  | IBD total |
|-------------|-------|-------|-------|-----------|
| Age at first diagnosis (years), mean (SD) | 20.5 (4.9) | 23.6 (6.0) | 26.2 (7.7) | 22.2 (5.9) |
| Disease extent according to Montreal classification | | | | |
| L1:L2:L3:L4 (n) | 8:13:4 | — | — | — |
| E1:E2:E3 (n) | — | 1:5:9 (n = 15) | — | — |
| Disease behavior according to Montreal classification (B1:B2:B3) (n) | 13:5:6 (n = 24) | — | — | — |
| Patients with their first pregnancy in the study period, n (%) | 9 (36) | 9 (56.3) | 1 (20) | 19 (41.3) |
| History of abdominal surgeries, n (%) | 14 (56) | 1 (18.8) | 1 (20) | 18 (39.1) |
| History of fistula surgeries, n (%) | 7 (28) | 0 | 0 | 7 (15.2) |
| History of IBD surgeries, n (%) | 8 (32) | 1 (6.3) | 0 | 9 (19.6) |

B: Baseline characteristics, courses and outcomes of the 50 included pregnancies

| Pregnancies (n) | CD    | UC    | IBDU  | IBD total |
|-----------------|-------|-------|-------|-----------|
| Age at beginning of pregnancy (years), mean (SD) | 29.6 (5.8) | 29.8 (5.8) | 30.7 (5.8) | 29.8 (4.1) |
| Disease duration to beginning of pregnancy (years), mean (SD) | 9.5 (5.5) | 6.4 (4.7) | 6.2 (4.7) | 8.1 (5.3) |
| Number of pregnancies per patient until observed pregnancy, median (range) | 2 (1–5) | 1 (1–3) | 3 (1–3) | 1.5 (1–5) |
| Current smoking at baseline, n | 0 | 0 | 0 | 0 |
| Maternal infections, n (%) | 8 (28.6) | 3 (18.8) | 2 (33.3) | 13 (26) |
| Documented disease activity at beginning of pregnancy, n (%) | 5 (17.9) | 2 (12.5) | 2 (33.3) | 9 (18) |
| Documented disease activity at any time during pregnancy, n (%) | 11 (39.3) | 13 (81.3) | 4 (66.7) | 28 (56) |
| HBI at beginning of pregnancy, mean (SD) | 0.8 (2.4) | — | — | 0.8 (2.4) |
| SCCAI at beginning of pregnancy, mean (SD) | — | 0.4 (1.3) | 1.0 (2.2) | 0.6 (1.5) |
| Active IBD during pregnancy, n (%) | 8 (28.6) | 12 (75.0) | 3 (50.0) | 23 (46.0) |
| Active IBD during 1st trimester, n (%) | 4 (14.3) | 3 (18.8) | 1 (16.7) | 8 (16.0) |
| Active IBD during 2nd trimester, n (%) | 3 (10.7) | 9 (56.3) | 1 (16.7) | 13 (26.0) |
| Active IBD during 3rd trimester, n (%) | 2 (7.1) | 5 (31.3) | 1 (16.7) | 8 (16.0) |
| Any IBD therapy during pregnancy, n (%) | 15 (53.6) | 15 (93.8) | 6 (100.0) | 36 (72.0) |
| Pregnancy duration in weeks, mean (SD) | 38.5 (3.2) | 37.1 (3.3) | 38.3 (1.0) | 38.0 (3.1) |
| Cesarean sections, n (%) | 18 (64.3) | 7 (43.8) | 1 (16.7) | 26 (52.0) |
| Birth weight in g, mean (SD) | 3041 (803) | 2728 (904) | 3295 (557) | 2975 (818) |
| Birth size in cm, mean (SD) | 50.2 (5.0) | 48.6 (4.5) | 50.2 (1.5) | 49.7 (4.7) |

Abbreviation: CD, Crohn’s disease; HBI, Harvey Bradshaw index; IBD, inflammatory bowel disease; IBDU, indeterminate colitis; SCCAI, simple clinical colitis activity index; SD, standard deviation; UC, ulcerative colitis.
significantly less than those who were born spontaneously (MD -602 g, CI -1040 to -161 g, p = 0.009). The mean birth size was 49.7 cm (SD: 4.7 cm; n = 46). Children originating from pregnancies with documented pregnancy complications were by 3.0 cm shorter than those originating from pregnancies without documented pregnancy complications (CI -5.8 to -0.2 cm, p = 0.042).

In contrast, active IBD at the beginning of pregnancy (birth weight: MD -117 g, CI -715 to 479 g, p = 0.701; birth size: MD -0.2 cm, CI -3.6 to 3.2 cm, p = 0.907), occurrence of active IBD during pregnancy (MD -309 g, CI -770 to 149 g, p = 0.196; MD -0.9 cm, CI -3.6 to 1.5 cm, p = 0.506), IBD-related therapy during pregnancy (-406 g, CI -1037 to 212 g, p = 0.164; -1.9 cm, CI -5.1 to 1.3 cm, p = 0.249), immunosuppressive therapy during pregnancy (-461 g, CI -991 to -63 g, p = 0.067; -1.5 cm, -4.3 to 1.2 cm, p = 0.267), or the occurrence of infection(s) during pregnancy (101 g, CI -453 to 656 g, p = 0.715; 1.4 cm, CI -1.8 to 4.6 cm, p = 0.392) did not influence birth weight and size significantly (Table 2).

Thirty-nine children were breastfed by their mothers (88.6%; n = 44).

**Adverse pregnancy outcomes**

Adverse pregnancy outcomes were reported in 14 of the 50 documented live births (28%). Overall, no chromosomal abnormalities or congenital malformations were noted.

Two newborns were SGA (4%), one was low birth weight (2%), two were preterm (4%), seven were low birth weight and preterm (14%), one was low birth weight, preterm, and SGA (2%), and one was born with high birth weight >4500 g (2%).

In the subgroup of pregnancies with documented pregnancy complications, 11 ended with adverse outcomes (35.5%, n = 31), while in the subgroup of pregnancies without pregnancy complications, 3 ended with adverse outcomes (20%, n = 15) (OR 2.22, CI 0.49–10.09, p = 0.303). Mixed model analyses did not reveal any statistically significant associations between the occurrence of adverse pregnancy outcomes and IBD activity in the beginning or at any time point during pregnancy (OR 1.89, CI 0.38–9.40, p = 0.437; OR 0.88, CI 0.26–2.99, p = 0.842), age of the pregnant patient (OR 1.01, CI 0.98–1.04, p = 0.425), active IBD during pregnancy (OR 1.12, CI 0.32–3.98, p = 0.856), pregnancy complications (OR 2.22,
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**TABLE 2** Factors with potential influence of birth weight and size

| Parameter                                      | Birth weight (g) | CI (g)       | p-value | Birth size (cm) | CI (cm) | p     |
|------------------------------------------------|------------------|-------------|---------|----------------|---------|-------|
| Cesarean section                               | −602             | −1040 to −161 | 0.009   | −2.1           | −4.7 to 0.5 | 0.121 |
| Pregnancies with documented pregnancy          | −417             | −923 to 88   | 0.113   | −3.0           | −5.8 to −0.2 | 0.042 |
| complications                                  |                  |             |         |                |         |       |
| Active IBD at beginning of pregnancy           | −117             | −715 to 479  | 0.701   | −0.2           | −3.6 to 3.2 | 0.907 |
| Occurrence of active IBD during pregnancy      | −309             | −770 to 149  | 0.196   | −0.9           | −3.6 to 1.5 | 0.506 |
| IBD-related therapy during pregnancy           | −406             | −1037 to 212 | 0.164   | −1.9           | −5.1 to 1.3 | 0.249 |
| Immunosuppressive therapy during pregnancy     | −461             | −991 to −63  | 0.067   | −1.5           | −4.3 to 1.2 | 0.267 |
| Occurrence of infections during pregnancy      | 101              | −453 to 656  | 0.715   | 1.4            | −1.8 to 4.6 | 0.392 |

Abbreviations: CI, confidence interval; IBD, inflammatory bowel disease.

CI 0.49–10.10, \( p = 0.303 \), any IBD therapy during pregnancy (OR 0.82, CI 0.19–3.34, \( p = 0.788 \)), immunosuppressive therapy during pregnancy (OR 1.55, CI 0.37–6.45, \( p = 0.548 \)), and maternal infection(s) during pregnancy (OR 1.24, CI 0.31–4.99, \( p = 0.761 \)).

**Postnatal child health and development**

Mean Apgar scores 1, 5, and 10 min after birth were 8.4 (SD: 0.9; range: 6–10; \( n = 30 \)), 9.6 (SD: 0.7; range: 8–10; \( n = 44 \)), and 9.8 (SD: 0.4; range: 8–10; \( n = 44 \)), respectively. Four newborns had an Apgar score of only 7 at 1 min; two of these newborns reached Apgar scores of 9 and 10 at 5 and 10 min, whereas the other two reached Apgar scores of 8 and 9 at 5 and 10 min, respectively. Apgar scores measured at different time points were not significantly influenced by IBD activity in the beginning or at any time during pregnancy, pregnancy complications, any IBD therapy during pregnancy, immunosuppressive therapy during pregnancy, and maternal infection(s) during pregnancy. However, they were at 1 and 5 min lower in pregnancies with pregnancy complications than in those without (1 min: 8.2 [SD: 1.0; \( n = 20 \)] vs. 8.9 [SD: 0.6; \( n = 8 \)], \( p = 0.078 \); 5 min: 9.5 [SD: 0.7; \( n = 29 \)] vs. 9.9 [SD: 0.3; \( n = 13 \)], \( p = 0.032 \); 10 min: 9.8 [SD: 0.7; \( n = 29 \)] vs. 10 [SD: 0; \( n = 13 \)], \( p = 1 \)).

Follow-up of 1 year was reached by 19 of the children (38%) while three (6%) were documented up to 48 months.

Developmental abnormalities and disorders were reported in 11 questionnaires (26.8%; \( n = 41 \)): in 10 children, one abnormality was described per child, while there was one child with several abnormalities indicated (for details, see Table 3).

IBD activity at the beginning of pregnancy (OR 2.48, CI 0.39–15.72, \( p = 0.336 \)), any documented disease activity during pregnancy (OR 3.05, CI 0.67–13.77, \( p = 0.148 \)), any IBD-related therapy (OR 0.66, CI 0.13–3.42, \( p = 0.624 \)), or immunosuppressive

**TABLE 3** List of health disorders documented for the children born to the mothers suffering from IBD during pregnancy

| Disease category          | Specification and frequency of disorder (n) | Immunosuppressive medication during pregnancy |
|---------------------------|--------------------------------------------|---------------------------------------------|
| Recurrent or severe infections | Recurrent respiratory infections (2) | Anti-TNFα (1) and none (1) |
|                           | Recurrent bronchitis and bladder infections (1) | Anti-TNFα |
|                           | Neonatal sepsis (1) | None |
| Skin diseases             | Ecema of the whole body (1) | None |
|                           | Neurodermatitis (1) | Systemic steroids and anti-TNFα |
|                           | Sun allergy (1) | Anti-TNFα |
| Chronic respiratory diseases | Exercise-induced asthma (1) | None |
|                           | Chronic bronchitis (1) | Systemic steroids & anti-TNFα |
| Hematological/immunological diseases | IgA-deficiency (1) | Anti-TNFα |
|                           | Acute leukemia (1) | Topic steroids |
| Neurological abnormalities | Tremor not further classified (1) | Systemic steroids & anti-TNFα |

Abbreviations: IBD, inflammatory bowel disease; TNFα, tumor necrosis factor alpha.

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medication (OR 1.34, CI 0.28–6.38, \( p = 0.714 \)) were not significantly associated with the occurrence of health disorders in the children.

Information on screening examinations of the newborns (“U1”) was available in 32 cases. Results of U8 examinations (performed between 46 and 48 months of age) were available only in three children. Table 4 summarizes the numbers of children examined, children reaching developmental milestones, and percentages of normally developed children in relation to all children examined at the respective time points. Sixty percent (9/15) of the children delivered via Cesarean section reached developmental milestones, while 82.4% (14/17) of the children delivered via spontaneous birth reached these milestones (OR 3.11, CI 0.62–15.71, \( p = 0.170 \)). Also, immunosuppressive therapy
during pregnancy or IBD activity during pregnancy did not influence the achievement of developmental milestones.

### Secondary Study Objectives

#### Pregnancy complications

Pregnancy complications were noted in 31 of 46 pregnancies (67.4%). Four pregnancies were not evaluated due to documentation reasons. The most prevalent among them was uterine bleeding in six cases (13.0%). All documented pregnancy complications and their rates are listed in detail in Table 5. Mixed model analyses failed to reveal significant differences concerning the frequency of pregnancy complications:

| Type of pregnancy complication     | Immunosuppressive medication during pregnancy |
|------------------------------------|-----------------------------------------------|
| Uterine bleeding                   | Anti-TNFα (1), thiopurine (1), topical steroids (1) |
| Hypersensitivity gravidarum        | Anti-TNFα (1), systemic steroids (1) |
| Gestational hypertension           | Anti-TNFα (3), thiopurine (1), systemic steroids (1) |
| Pre-eclampsia                      | Anti-TNFα (3), thiopurine (1) systemic steroids (1) |
| Gestational diabetes               | Anti-TNFα (2), systemic steroids (1) |
| HELLP syndrome                     | Anti-TNFα (1), thiopurine (1), systemic steroids (1) |
| Fetal growth restriction           | Anti-TNFα (1), systemic steroids (1) |
| Pregnancy cholestasis              | Thiopurine (2) |
| Cervical insufficiency             | — |
| Abnormal fetal heart rates on CTG  | Systemic steroids (1) |
| Polyhydramnios                     | Anti-TNFα (1), topic steroids (1) |
| Oligohydramnios                    | Anti-TNFα (1) |
| Uterine artery flow notching on ultrasound | Anti-TNFα (1) |
| Premature labor                    | — |
| Maternal urinary tract obstruction  | — |

Abbreviations: HELLP, hemolysis, elevated liver enzymes, low platelet count; CTG, cardiotocography; TNFα, tumor necrosis factor alpha.

### Table 4

| Children (n, %) | CD | UC | IBD-U | IBD total |
|----------------|----|----|-------|-----------|
| U1 (directly after birth) | 19 (67.9) | 8 (50) | 4 (66.7) | 31 (62.0) |
| U2 (3–10 days) | 15 (53.6) | 7 (43.8) | 4 (66.7) | 26 (52.0) |
| U3 (4–5 weeks) | 15 (53.6) | 7 (43.8) | 4 (66.7) | 26 (52.0) |
| U4 (3–4 months) | 13 (46.4) | 7 (43.8) | 4 (66.7) | 24 (48.0) |
| U5 (6–7 months) | 13 (46.4) | 7 (43.8) | 4 (66.7) | 24 (48.0) |
| U6 (10–12 months) | 11 (39.3) | 6 (35.7) | 2 (33.3) | 19 (38.0) |
| U7 (21–24 months) | 8 (28.6) | 3 (18.8) | 2 (33.3) | 13 (26.0) |
| U7a (34–36 months) | 5 (17.9) | 1 (6.3) | 1 (16.7) | 7 (14.0) |
| U8 (46–48 months) | 2 (7.1) | 0 (0) | 1 (16.7) | 3 (6.0) |
| Achievement of developmental milestones | 12 (42.9) | 7 (43.8) | 4 (66.7) | 23 (46) |
| Normally developed children (%) | 12 (63.2), n = 19 | 7 (77.7), n = 9 | 4 (100), n = 4 | 23 (71.9), n = 32 |

### Table 5

| n = 46 (%) | Type of pregnancy complication     | Immunosuppressive medication during pregnancy |
|------------|------------------------------------|-----------------------------------------------|
| 6 (13.0)   | Uterine bleeding                   | Anti-TNFα (1), thiopurine (1), topical steroids (1) |
| 5 (10.9)   | Hypersensitivity gravidarum        | Anti-TNFα (1), systemic steroids (1) |
| 5 (10.9)   | Gestational hypertension           | Anti-TNFα (3), thiopurine (1), systemic steroids (1) |
| 5 (10.9)   | Pre-eclampsia                      | Anti-TNFα (3), thiopurine (1) systemic steroids (1) |
| 4 (8.7)    | Gestational diabetes               | Anti-TNFα (2), systemic steroids (1) |
| 3 (6.5)    | HELLP syndrome                     | Anti-TNFα (1), thiopurine (1), systemic steroids (1) |
| 3 (6.5)    | Fetal growth restriction           | Anti-TNFα (1), systemic steroids (1) |
| 2 (4.3)    | Pregnancy cholestasis              | Thiopurine (2) |
| 2 (4.3)    | Cervical insufficiency             | — |
| 2 (4.3)    | Abnormal fetal heart rates on CTG  | Systemic steroids (1) |
| 2 (4.3)    | Polyhydramnios                     | Anti-TNFα (1), topic steroids (1) |
| 2 (4.3)    | Oligohydramnios                    | Anti-TNFα (1) |
| 1 (2.2)    | Uterine artery flow notching on ultrasound | Anti-TNFα (1) |
| 1 (2.2)    | Premature labor                    | — |
| 1 (2.2)    | Maternal urinary tract obstruction  | — |

Abbreviations: HELLP, hemolysis, elevated liver enzymes, low platelet count; CTG, cardiotocography; TNFα, tumor necrosis factor alpha.

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documented disease activity at the beginning or during pregnancy versus no disease activity (OR 0.81, CI 0.23–2.83, p = 0.741); occurrence of at least one time point with active IBD during pregnancy versus no activity (OR 1.60, CI 0.46–5.59, p = 0.461); any IBD-related medication during pregnancy versus no IBD-related medication (OR 1.52, CI 0.36–6.46, p = 0.574); and immunosuppressive therapy during pregnancy versus no immunosuppressive therapy (OR 0.91, CI 0.25–3.34, p = 0.886). Pregnancy complications were not significantly more likely to occur during pregnancies with documented maternal infections than during those without (OR 9.85, CI 0.85–114.56, p = 0.068).

**Pregnancy duration**

The mean pregnancy duration of 48 evaluated pregnancies was 38 weeks (SD: 3.1 weeks). Due to documentation reasons, we had to exclude two pregnancies from this specific statistical analysis. Pregnancies of mothers with proof of any IBD activity during pregnancy tended to be shorter than pregnancies of mothers without any documented IBD activity (MD −1.53 weeks, CI −3.27 to 0.20 weeks; p = 0.089). In mixed model analysis, pregnancy duration was not significantly associated with active IBD at the beginning of pregnancy (MD −0.3 weeks, CI −2.6 to 1.9 weeks; p = 0.78), occurrence of active IBD during pregnancy (MD −1.3 weeks, CI −3.0 to 0.5 weeks; p = 0.166), IBD-related therapy during pregnancy (MD −0.7 weeks, CI −2.8 to 1.5 weeks; p = 0.528), immunosuppressive therapy during pregnancy (MD −1.1 weeks, CI −2.9 to 0.8 weeks; p = 0.268), or the occurrence of infection(s) during pregnancy (MD 0.5 weeks, CI −1.6 to 2.6 weeks; p = 0.663). Children delivered by Cesarean section were born 1.9 weeks earlier than those delivered by spontaneous birth (CI −3.6 to −0.3 weeks, p = 0.029).

**Discussion**

**Main results and comparison with literature**

The present study reports on the outcomes of 50 live births from 46 patients observed at a single IBD tertiary referral center located in Southwest Germany. The main study focus—corresponding to its primary study objective—was a description of early postnatal child development of children born to mothers with IBD. Its key findings are that early postnatal child health and development were not significantly influenced by either IBD activity or IBD drug exposure during pregnancy.

Several previously published studies revealed that pregnant women with IBD were at increased risk of adverse birth outcomes, such as stillbirth, growth retardation and preterm birth, particularly if they suffered from repeated IBD flares throughout pregnancy. A recently published meta-analysis of 53 studies which included 7917 IBD pregnancies and 3253 healthy control pregnancies found that gestational diabetes and pre-term pre-labor rupture of membranes occurred more frequently in IBD patients than in healthy controls. In addition, Cesarean delivery was a more common event in IBD patients compared to healthy controls (OR 1.79, 95% CI 1.16–2.77).

Unfortunately, it was not possible to include a healthy control group in our study. Therefore, our data can only be compared to those from existing literature or birth registries.

In Germany, the rate of preterm births was 9.2% in 2012 and 8.6% in 2016, which corresponds roughly to the time interval when our data were collected. At 17%, the rate of preterm births was nearly twice as high as in our cohort of pregnant women with IBD compared to the general population. Also, with 52%, we observed a high rate of Cesarean deliveries in our cohort. In comparison, rates of Cesarean delivery are in general around 30% in German hospitals. In a recent Canadian retrospective cohort study, Cesarean delivery rates in women with CD were 52% and with UC 48%, which are in conformity to our own results. In that study, the strongest predictors for the performance of Cesarean sections were a history of perianal disease and prior Cesarean delivery. The fact that the rate of Cesarean deliveries was by ca. 22% higher in our study as compared to that in the general population suggests that the difference should be explainable by the condition of IBD during pregnancy.

Nearly 89% of the patients for whom this piece of information was available initiated breastfeeding of their babies. In a Canadian population-based study published in 2009 which included 156 live births by women with IBD, the rate of breastfeeding initiation was 83.3% versus 77.1% in the general population (p > 0.05). Given the fact that a recent meta-analysis considering 35 studies revealed that breastfeeding protected against the development of CD and UC, this is an encouraging result, and IBD patients should be recommended to breastfeed their babies.
Subgroup analysis within the cohort of pregnant IBD patients was performed and revealed that outcomes including pregnancy complications, birth outcomes, and early child health and development were not significantly different depending on whether or which IBD medication(s) were used by the women during their pregnancies. This confirms the findings of previous studies. However, a tendency of lower birth weight and birth size was seen in patients with IBD-related therapy during pregnancy (birth weight: MD = 406 g; birth size: MD = 1.9 cm). Medications included in our study were mainly steroids, thiopurines, and TNFα inhibitors; the latter usually being paused around week 22 of pregnancy, if possible. Pregnancies with any maternal IBD activity tended to be shorter than pregnancies of mothers without any documented IBD activity (37.4 vs. 38.9 weeks, MD = 1.53 weeks), and showed a lower birth weight (MD = 309 g) and smaller birth size (MD = 0.9 cm). Potentially due to the small patient group, our data did not reach significance in contrast in previous studies. On the other hand, there are also recent studies, like the study of de Lima-Karagiannis et al., which did not confirm the higher risk of adverse pregnancy and birth outcomes in pregnant IBD patients with active disease. This may be an effect of the growing knowledge and awareness of potential pitfalls in IBD pregnancies, which might be able to compensate for naturally adverse courses of pregnancy in IBD. The primary study objectives of this study were to explore whether children born to mothers with IBD showed any abnormalities or problems directly after birth or in their early development. No congenital abnormalities or deaths were noted in the offspring of our cohort of IBD patients. Mean Apgar scores 1, 5, and 10 min after the birth were 8.4, 9.6, and 9.8, respectively. The Apgar score is the most routinely employed measure of health status for newborns. In a recent population-based cohort study from Sweden, only 11% of term infants had an Apgar score of 10 at 1 min, while 89% and 97% had a score of 10 at 5 and 10 min, respectively. Even the children of our cohort who had Apgar scores ≤7 reached scores of at least 8 at 5 and 10 min.

Even though we had no control group for comparison, we may conclude from our data that postnatal and early childhood health and development were not conspicuous in our cohort. Also, being fully aware that subgroups available for analyses were weakly powered, no significant differences were found between children of mothers with active IBD and inactive IBD, or in relation to IBD medications during pregnancies.

Investigating the influence of pregnancy on the course of IBD was not the focus of the present study. An interesting observation, however, was that disease relapses occurred more often in pregnancies of women with UC than of those suffering from CD. Similar findings were reported by de Lima-Karagiannis et al. in their study including 298 pregnancies in 229 IBD patients.

Strengths and limitations of this study
The main strength of this study is that the analyzed data were recruited from different data sources. Thus, it was possible in a large part of the patients to assemble a complete picture of IBD during pregnancy as well as of birth outcomes and child development in their early years of life. This would not have been feasible without the inclusion of the questionnaires and the copies of official gynecological and pediatric screening documents. The most distinctive feature of the study is that it included data from the observed pregnancies as well as data from the born children in their early development. This is of great relevance because potential mothers with IBD and their physicians may tend to consider the child’s health and development a priority, to the possible detriment of the mother’s well-being.

However, there are also important limitations to the study: first of all, this is a retrospective study with a relatively small patient number. Thus the statistical power is low, and the generalizability of the outcomes is limited. Furthermore in the statistics for the secondary study objectives, four patients had to be excluded from the evaluation of pregnancy complications and two patients from the evaluation of pregnancy duration, which reduced the small patient number even more. Also, the study carries a relatively high risk of selection bias. By only including patients of a tertiary referral center treating especially IBD patients with complex disease courses, the resulting pregnancy outcomes may be worse than those expected for the general IBD population. Another type of selection bias relevant for the interpretation of the study results was the nonresponse bias. For the questionnaires, the response rate of the included patients was 80%, but only 52% of patients submitted their copies of medical screening documents. We suggest that there may have been two reasons why patients did not send copies of the screening documents: first, it took more effort than just filling in the questionnaires, especially if the patients had no copy machine at hand; second, patients may have had the feeling that giving away copies of their screening documents for a study was too invasive of their privacy.
IBD activity and medications did not significantly influence birth, postnatal health, and development of the children in our study. However, the result should be interpreted with caution due to relatively small sample sizes.

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Author Contributions

Peter Hoffmann and Annika Gauss conceived of the idea of the manuscript and supervised the project. Peter Hoffmann, Annika Gauss, and Julian Krueger collected, analyzed, and interpreted data and wrote the manuscript. Lukas Baumann helped with statistical analyses. Teodora Bashlekova and Christian Rupp collected data. All authors discussed the results and commented on the manuscript.

Disclosure

None of the authors have conflicts of interest to declare.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Supplementary Table S1 Therapies during pregnancy