

Placental inflammation is not increased in inflammatory bowel disease

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Abstract

Background Women with inflammatory bowel disease (IBD) are at increased risk for adverse birth outcomes such as preterm delivery and small for gestational age (SGA) infants. Most recognized cases of fetal growth restriction in singleton pregnancies have underlying placental causes. However, studies in IBD examining poor birth outcomes have focused on maternal factors. We examined whether women with IBD have a higher rate of placental inflammation than non-IBD controls.

Methods Between 2008 and 2011, the placental tissue of 7 ulcerative colitis, 5 Crohn's disease, and 2 IBD-unclassified subjects enrolled in the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcome (PIANO) registry were evaluated for villitis, deciduitis, and chorioamnionitis with/without a fetal inflammatory response. The history and birth outcomes of all IBD subjects were reviewed and matched to 26 non-IBD controls by gestational age at delivery.

Results Of women with IBD, 29% delivered preterm infants and 21% delivered SGA infants. Half of the IBD patients had mild-moderate disease flares during pregnancy. Five (36%) patients required corticosteroids, 2 (14%) were maintained on an immunomodulator, and 3 (21%) others received tumor necrosis factor-alpha inhibitors during their pregnancy. Chorioamnionitis was the only identified placental pathology present in the placentas reviewed, occurring less frequently in cases compared to controls (7% vs. 27%, P=0.32).

Conclusions Placental inflammatory activation does not appear to be responsible for the increase in adverse birth outcome in women with IBD. Further studies are necessary to validate these findings in IBD to explain poor birth outcomes.

Keywords Inflammatory bowel disease, pregnancy, placenta, pathology, birth outcome

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Introduction

The incidence and prevalence of inflammatory bowel disease (IBD) is increasing worldwide [1]. The peak incidence of the inflammatory bowel diseases, ulcerative colitis (UC) and Crohn's disease (CD), occurs between the ages of 15-29 [2,3]. This period overlaps with the peak time for pregnancy. While disease quiescence at the time of conception is a predictor for ongoing disease inactivity during pregnancy, at least one-third of women with IBD who are in remission experience an exacerbation of their disease during pregnancy [4]. Women with active disease may be at greatest risk for poor birth outcomes. It is important to note, however, that studies have shown that even among women with quiescent IBD throughout pregnancy, the rate of adverse birth outcomes is higher compared to the general population [5]. Thus better understanding of the factors

which may contribute to birth outcomes of women with IBD is needed such that targets for interventions aimed at improving neonatal well-being can be developed [5-8].

Most studies have shown an increased risk for fetal growth restriction and preterm delivery in women with IBD [5-8]. Among non-IBD patients, these birth outcomes can generally be attributed to maternal, fetal, or placental factors. Maternal factors refer to a deficiency in nutrient and oxygen delivery to the placenta whereas fetal factors relate to abnormal nutrient uptake leading to dysregulated growth. Umbilical-placental vascular anomalies, placenta previa, placental infarction, placental abruption, placental infection, and multiple gestations are categorized as placental factors. In the general population after excluding constitutional small for gestational age (SGA) infants, most recognized cases of fetal growth restriction in singleton pregnancies have underlying placental causes that arise from nutrient and oxygen transfer across the placenta [9-11].

To date, studies showing an increased risk for poor birth outcomes in women with IBD have attributed their findings mainly to maternal factors such as disease activity, IBD medication use, and nutritional deficiency [12-14]. Placental factors in growth restriction among women with IBD have not been well studied. In fact, no published data is currently available examining the placental histology of these women. Thus, the purpose of this study was to compare placental histology of women with IBD to that of women without IBD. We hypothesized that there is an increased rate of placental inflammation in women with IBD who have poor birth outcomes.

Materials and Methods

We retrospectively reviewed the medical records of women with IBD enrolled in the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry at Women and Infants Hospital (WIH) in Providence, Rhode Island. PIANO is a prospective cohort of pregnant women at 30 IBD centers in the United States designed to determine whether medication exposure affects complication rates [15]. Pregnant women with IBD are prospectively enrolled and contacted every trimester, at the birth of their baby, and when the infant is 4, 9, and 12 months of age. Newborn complications and the mothers' medications along with complications of pregnancy and delivery are recorded. WIH has served as a site of enrollment since 2007. The study was conducted with the approval of the WIH institutional review board (IRB) and in compliance with the Health Insurance Portability and Accountability Act (HIPAA). All subjects provided informed consent prior to involvement in the study.

Subjects

Subjects enrolled in PIANO who gave birth between March 2008 and April 2011 at WIH were included in this study. A control group consisted of women without IBD or other major co-morbidities who delivered at WIH during the same time

period. The controls, obtained from files of WIH Department of Pathology, were matched by gestational age to cases.

Demographic factors, medical and obstetric histories, fetal body weight, placental weight, mode of delivery, medication profiles as well as pregnancy course and birth outcomes for subjects also were documented.

IBD disease activity was assessed using a combination of clinical symptoms, labs, radiographic studies, and endoscopic findings. A modified version of the American College of Gastroenterology Guidelines for CD and UC was utilized to classify disease activity into one of four categories: remission, mild, moderate, or severe (Table 1) [16, 17].

Placenta

Placental inflammation is categorized by its location and type of inflammation: acute, subacute, or chronic. Acute chorioamnionitis with or without a fetal inflammatory response, villitis, and deciduitis are the most common types of placental inflammation (Table 2).

In this study, placental and umbilical cord histology was reviewed by two, blinded perinatal pathologists for evidence of inflammation and classified according to previously published criteria (Table 2) [18]. A Mann-Whitney *U* test (GraphPad Software™) was used to compare placental histology findings between IBD and non-IBD mothers. Statistical significance was defined as $P < 0.05$.

Results

During the study period 36 subjects were enrolled in PIANO at WIH. Fourteen subjects delivered at WIH and had placental tissue available for review. Twenty-six women served as controls.

Subject demographics

Subjects ranged in age from 21 to 42 years. The mean age at conception was 32.4 (± 4.8) years for cases. All subjects except one

Table 1 Inflammatory bowel disease activity classification (adapted from ref. 15, 16)

Remission	Clinically asymptomatic without inflammatory sequelae
Mild	Ambulatory but symptomatic without dehydration, high fevers or rigors, abdominal pain or masses, intestinal obstruction, or >10% weight loss
Moderate	More persistent fevers with abdominal pain, >10% weight loss, or significant anemia
Severe	Persistent symptoms despite corticosteroids or biological agents and may have high fevers, evidence of obstruction, significant peritoneal signs, cachexia, or abscess

were Caucasian. All subjects denied smoking during pregnancy and only one subject reported alcohol use during pregnancy. The median gravida per subject was 1.4 (range 0-6) and median parity was 0.5 (range 0-3). Nine of the IBD mothers delivered at term (i.e., between 37-42 weeks gestation), 1 had a late preterm delivery (i.e., between 34-36 weeks), and 4 had early preterm deliveries (i.e., before 34 weeks). Fifteen of the non-IBD mothers delivered at term, 4 had late preterm deliveries, and 7 had early preterm deliveries. Among women with IBD, the distribution of the disease subtype was as follows: 7 (50%) had UC, 5 (36%) had CD, and 2 (14%) had IBD-unclassified (IBD-U). Demographic and disease data for cases is summarized in Table 3.

Disease activity and medication use

Five subjects had a moderate exacerbation of their disease during pregnancy while one had a mild exacerbation (Table 3). Four of the five subjects with moderate exacerbation of disease were placed on corticosteroids. One subject diagnosed with *de novo* CD in the third trimester also was treated with corticosteroids and metronidazole. Nine subjects were treated with oral or topical mesalamine. The 2 subjects treated with an immunomodulator (i.e., azathioprine or 6-mercaptopurine) and 2 of the 3 treated with a tumor necrosis factor (TNF)- α inhibitor were started on their medication prior to pregnancy. One subject was changed from adalimumab to certolizumab at 30 weeks gestation and another subject discontinued her infliximab at 30 weeks gestation. One subject was started on certolizumab pegol during her pregnancy due to a moderate disease flare. At the time of conception, all IBD patients were clinically asymptomatic though four were corticosteroid dependent. Two subjects took no medications for their IBD during the course of their pregnancy.

Summary of outcomes

All IBD and non-IBD subjects had singleton pregnancies that resulted in live births. There were no congenital anomalies. Eight (57%) of the IBD mothers underwent Cesarean sections. Two IBD patients had pregnancies complicated by preeclampsia and 4 developed gestational diabetes.

Among the 26 non-IBD subjects, eleven (42%) pregnancies resulted in preterm deliveries, five (19%) had SGA births, and two (8%) had large for gestational age births as it is used only once births.

Placental weight and histology

Twelve of fourteen cases (86%) had SGA placentas defined as placental weights below the 10th percentile after accounting for gestational age (Table 4) [19,20]. The fetal to placental weight ratios for cases however fell within the expected range [19,20].

Acute chorioamnionitis (ACA) was found in 1 of 14 placentas (7%) from subjects with IBD compared to 27% of the

Table 2 Inflammatory lesions of the placenta (adapted from Table in ref. 17)

Site and type	Histological pattern
Deciduitis <i>Acute / subacute</i> <i>Chronic</i>	None Diffuse lymphocytic Focal lymphoplasmacytic
Chorioamnionitis <i>Acute</i> <i>Subacute / chronic</i>	Stage 1: acute subchorionitis / chorionitis Stage 2: chorioamnionitis Stage 3: necrotizing chorioamnionitis Mixed neutrophilic-histiocytic chorioamnionitis
Fetal <i>Acute</i> <i>Subacute / chronic</i>	Stage 1: chorionic vasculitis / umbilical phlebitis Stage 2: umbilical arteritis Stage 3: umbilical perivasculitis Subnecrotizing or necrotizing funisitis / perivasculitis
Villitis <i>Acute</i> <i>Chronic</i>	With intervillous abscesses With fetal sepsis Diffuse placentitis Villitis of unknown etiology with/without obliterative fetal vasculopathy

control placentas (P=0.32). The IBD patient with ACA had a moderate flare during her pregnancy requiring corticosteroids and remained corticosteroid-dependent with resolved symptoms at conception. The IBD placenta with ACA also had funisitis suggestive of a fetal inflammatory response to ACA in one of the umbilical arteries. Only one of the seven non-IBD placentas with ACA had umbilical cord arteritis. No clinically significant cases of placental villitis or deciduitis were observed in either group. Other than vasculitis in the case with ACA and one of the controls with ACA, no other subjects had evidence of umbilical cord abnormalities. The concordance rate between the two blinded pathologists was 100%.

Discussion

Pregnant women with IBD, irrespective of medical treatment or in some cases disease activity, are at increased risk for such adverse birth outcomes as spontaneous abortion, low birth weight and SGA. infants, and preterm delivery [5-7,14]. Placental histological findings such as chronic villitis and deciduitis and ACA repeatedly have been associated with preterm birth, spontaneous abortion, and intrauterine growth retardation [21-24]. Prior studies have documented a significant increase in placental pathology in a variety of immune-mediated diseases including autoimmune thyroid disease, idiopathic thrombocytopenic purpura, and multiple sclerosis [25,26]. Prior to this study placental histology had not been examined to determine its association

Table 3 Age and IBD medications of cases

Subject ^A	Age ^B	IBD subtype	Meds prior to pregnancy ^C	Severity/timing of flare	Meds started during pregnancy ^D
101	28	UC	Balsalazide	Moderate in 3 rd trimester	Prednisone 40 mg
102	32	CD	Azathioprine 100 mg, Mesalamine, Hydrocortisone foam	Moderate in 2 nd trimester	Prednisone ^E , Valacyclovir
103 ^E	28	CD	None	Moderate in 3 rd trimester	Prednisone 40 mg, Metronidazole 1500 mg, Clindamycin ^F (unknown duration), Famotidine 10 mg
104	34	UC	Mesalamine	N/A	None
105	30	UC	Mesalamine oral and enema	Moderate in 1 st trimester	Prednisolone 120 mg ^G , Prednisone 60 mg ^H
106	42	UC	Metoprolol 25 mg	N/A	None
107	36	CD	Adalimumab 40 mg Q2wk ^I , Glburide 5mg, ASA 81 mg	N/A	Certolizumab 400 mg Q4wk ^I
108	23	UC	Mesalamine oral	N/A	None
109	32	UC	6-MP ^K , Mesalamine oral and suppository, Hydrocortisone enema, Insulin	Moderate in 3 rd trimester	Prednisolone ^{E,G} , Prednisone ^H
110	31	IBD-U	Infliximab at unknown dose Q8wk ^L , Mesalamine oral and enema	N/A	None
111	39	CD	Insulin	Moderate in 2 nd trimester	Certolizumab 400 mg Q4wk ^L
112	30	CD	Balsalazide, Albuterol, Fluvoxamine ^F	N/A	None
113	33	UC	Mesalamine oral and suppository, Ursodiol ^F	Mild in 3 rd trimester	None ^M
114	35	IBD-U	None	N/A	None

^AAll patients were nonsmokers and all patients with the exception of subject 109 did not drink alcohol through their pregnancy; ^BMean age is 32.4; median age is 32; ^CTaken for >4 weeks during pregnancy. Unless otherwise noted patients continued medication at specified total dose per day throughout pregnancy; ^DUnless otherwise noted, patient continued medication at specified total dose per day throughout pregnancy; ^ETapered off during pregnancy; ^FDiagnosed with Crohn's disease during 3rd trimester; ^GUnknown dose; ^HTransitioned to oral steroid; ^ITapered to 20 mg and continued for remainder of pregnancy; ^JStopped at 30 wks gestation; ^KStarted at 30 wks gestation; ^LStopped in 3rd trimester; ^MStarted in second trimester; ^NDose of topical mesalamine was increased to manage mild flare. IBD-U, inflammatory bowel disease-undefined

with poor birth outcomes in women with IBD. Our results indicate that placental pathology may not be increased in these patients. In fact, our data suggest chorioamnionitis may occur less frequently in placentas of women with IBD compared to women without IBD.

Placental inflammatory lesions affect the chorion, amniotic fluid, decidua, placental villi, and fetal vessels (Table 2). ACA is a major cause of spontaneous preterm birth and histologically it is defined by presence of acute inflammatory cell infiltration within placental chorioamnion and umbilical cord. The maternal inflammatory response precedes the fetal response and it is characterized by infiltration of chorionic plate and placental membranes by maternal neutrophils [21]. Transmigration of neutrophils from umbilical cord or chorionic vessels represents fetal inflammatory response and this can go through a series of quantifiable stages. Hematogenous infections usually give rise to acute villitis, characterized by neutrophilic infiltration of villous stroma, capillaries and intervillous space. Chronic villitis is defined as presence of chronic inflammatory cells infiltrating the terminal villous stroma. The etiology of chronic villitis is still unknown, but it is thought to be immune mediated. It can be seen in association

with chronic deciduitis, which is diagnosed when chronic inflammatory infiltrate in decidua basalis is identified. Chronic deciduitis is usually associated with genital tract infections.

ACA, a clinical or histological diagnosis commonly occurring after prolonged premature rupture of membrane, is typically due to a polymicrobial infection secondary to ascending bacteria from the genitourinary tract, gastrointestinal (GI) tract, skin, or oral cavity. *Ureaplasma urealyticum* and *Gardnerella vaginalis* are the 2 most commonly cultured organisms from placentas of women with ACA [27]. Since the composition of the microbial environment in the gut differs in individuals with IBD compared with those without IBD [28-30], translocation of bacteria from the GI tract to the urovaginal tract may result in a different bacterial milieu. Even in the setting of immunosuppression this bacterial composition may make IBD mothers less susceptible to ACA. In addition to microbial factors, certain genetic factors may increase the risk of ACA. For example, specific TNF- α genes may make individuals genetically susceptible to chorioamnionitis and therefore inhibition of this cytokine could decrease the probability of ACA [31]. Three of the 14 IBD patients in this study were on anti-TNF agents which may have protected them from ACA.

Table 4 Characteristics of pregnancies, placentas and fetuses in cases

Subject ^A	Obstetric history ^B	Gestational age	Mode of delivery ^C	Placental weight in grams ^D	Birth weight	Fetal to placenta weight ratio ^E
101	G1P1	33	SDV	292	SGA	7.77
102	G4P1	Term	C/S	570	AGA	6.93
103	G1P1	Term	C/S	458	SGA	8.80
104 ^F	G2P2	32	SVD	314	SGA	6.86
105 ^G	G1P1	33	SVD	252	AGA	7.08
106	G2P2	Term	C/S	356	AGA	7.96
107	G3P1	Term	C/S	331	AGA	10.0
108	G4P2	31	SVD	309	AGA	4.95
109	G2P1	Term	C/S	481	AGA	7.72
110	G1P1	Term	SVD	461	AGA	8.35
111	G7P4	Term	SVD	488	AGA	7.84
112	G2P2	Term	C/S	434	AGA	7.58
113	G2P1	Term	C/S	495	AGA	7.68
114	G2P1	35	C/S	383	AGA	6.66

SVD, spontaneous vaginal delivery; C/S, C-section; SGA, small for gestational age; AGA, appropriate for gestational age. ^ANo patient except 105 had any evidence of placental histological evidence of chorioamnionitis, villitis, or deciduitis; ^BMean gravida is 2.4 and mean parity was 1.5; Median gravida was 2 and median parity was 1; ^CAll C-sections were scheduled except for 109 who underwent C-section for rupture of membrane; ^DPlacental weights account for gestational age and gender (cite); all placental weights fell below the 10th percentile except subjects 102 and 113; ^EAll ratio values are based on gestational age and fell within the expected range; ^FPatient had prolonged premature rupture of membrane (PPROM); no other patients had PPROM; ^GPlacental histology consistent with Stage I chorioamnionitis with Stage II fetal inflammatory response seen in one artery of umbilical cord

Small placental size and fetal body weight to placental ratio has been associated with fetal growth impairment [32]. In this study, 86% of the cases met the criteria for SGA placentas. Placental weight also has been evaluated in other autoimmune diseases like systemic lupus erythematosus where renal involvement is associated with a lower mean placental weight [33]. The efficiency of placenta to transfer nutrients to the fetus is an important determinant of fetal size and can be measured indirectly as fetal body weight to placental weight ratio. Despite a high prevalence of SGA placentas, fetal body weight to placenta ratio among cases fell within a normal range suggesting there may be increased IBD placental efficiency. This is consistent with studies showing that in normoxic conditions before term, lighter placentas have higher efficiency than heavier placentas due to the fetal drive to obtain nutrients [34].

One strength of this study is that two blinded pathologists reviewed all placentas. Interobserver variability of placental histopathologic diagnosis has been found to be good to excellent. In one study of two pathologists examining 250 placentas for inflammatory lesions including ACA and villitis, the kappa values ranged from 0.70-0.83 [35]. The concordance rate in our study of 40 placentas was 100%. Other studies examining a similar number placentas found lower percentage agreement rates for chronic deciduitis (76%) and kappa value for ACA (0.83) [36,37]. However, these studies involved at least five pathologists and more frequent placental lesions compared to our study.

Despite the lack of placental inflammation, the SGA and preterm delivery rate of the IBD subjects in our study (21%

and 36%, respectively) were higher than those that have been previously reported. In a population-based cohort from Washington state, Dominitz *et al* found that women with CD when compared to non-IBD controls had a pre-term delivery rate of 15.2% (vs. 7.2% in non-IBD controls), LBW delivery rate of 16.8% (vs. 5.3%), and a SGA rate of 15.2% (vs. 6.9%) [6]. Similarly, using a population-based cohort of pregnant women with IBD in northern California, Mahadevan *et al* found that women with IBD regardless of disease activity had a pre-term delivery rate of 14.2% (vs. 9.6% for controls) and SGA rate of 12% (vs. 10% for controls) [5]. Several factors may have contributed to the differences in SGA and preterm rates in our cohort compared to prior studies. First, advanced maternal age is a known risk factor preterm and SGA infants. In our IBD cohort, the mean age of women at conception was 32.4 which is higher than the mean age for the women in the previously cited studies [5,6]. In addition, disease activity may have been greater in our subjects. Only the study by Mahadevan *et al* took into account disease activity when evaluating pregnancy outcomes. In that cohort of pregnant women immunosuppressants were used by only 4% and corticosteroids were used by 21% [5]. In comparison, in our study 36% of patients were on immunomodulators and/or an anti-TNF- α agent and 36% were on an oral corticosteroid during their pregnancy. This suggests that baseline disease severity and disease activity during pregnancy may have been greater in our population. Because WIH is one of the nation's leading specialty hospitals for women and newborns and serves as a referral center for high-risk pregnancies, selection

Summary Box

What is already known:

- Women with inflammatory bowel disease (IBD) are at increased risk for poor birth outcomes
- Most cases of fetal growth restriction in singleton pregnancies have underlying placental causes
- Studies in pregnancy and IBD have focused on maternal factors to explain poor birth outcomes

What the new findings are:

- Placental inflammation does not appear to be responsible for poor birth outcomes in IBD
- Chorioamnionitis may occur less frequently in placentas of women with IBD
- Further studies are necessary to examine the role of placental inflammation in poor birth outcomes in IBD

bias may have contributed to the higher SGA and preterm delivery rates seen in our study.

Inadequate maternal nutrition and active disease consistently have been associated with poor birth outcomes in women with IBD [12,38,39]. Medications used in IBD also have been implicated [13,14]. However, with the exception of methotrexate, the medications typically used to treat IBD such as 5-aminosalicylates, corticosteroids, immunomodulators, and anti-TNF- α agents generally have been deemed compatible for use during pregnancy [15,40]. Other maternal factors linked with adverse birth outcomes in women with IBD include smoking and high circulating prostaglandin levels [12,14,41].

In this study the rate of placental pathology defined as villitis, deciduitis, and chorioamnionitis was not higher in an IBD cohort compared to gestational-age matched non-IBD controls. The low rate of inflammatory lesions may be attributable to selection bias since all cases were enrolled in the PIANO registry and were being closely monitored by a team of gastroenterologists, obstetricians, and perinatologists and had their disease aggressively controlled. Nevertheless, although few inflammatory lesions were identified, the preterm birth and SGA rates were elevated in our cohort compared to rates in the literature suggesting disease severity and disease activity may have been higher in our population compared to the general pregnant IBD population.

The sample size in this study does not allow for definitive conclusions. However, our analysis suggests limited placental pathology in pregnant women with IBD. Rates of preterm delivery and SGA, however, were higher than what has been reported in the literature. Further studies are necessary to examine placental pathology as a cause of adverse birth outcomes in women with IBD.

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