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Pregnancy and Neonatal Outcomes After Fetal Exposure to Biologics and Thiopurines Among Women With Inflammatory Bowel Disease

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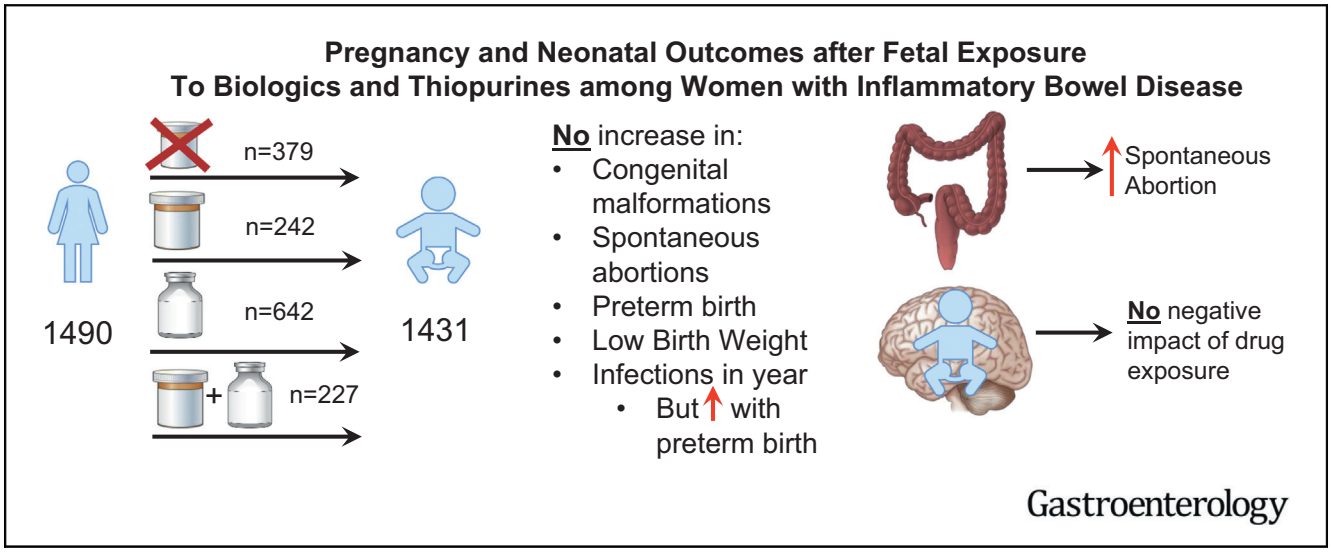

BACKGROUND & AIMS: Pregnant women with inflammatory bowel disease (IBD) may require biologic or thiopurine therapy to control disease activity. Lack of safety data has led to therapy discontinuation during pregnancy, with health repercussions to mother and child. **METHODS:** Between 2007 and 2019, pregnant women with IBD were enrolled in a prospective, observational, multicenter study across the United States. The primary analysis was a comparison of 5 outcomes (congenital malformations, spontaneous abortions, preterm birth, low birth weight, and infant infections) among pregnancies exposed vs unexposed in utero to biologics, thiopurines, or a combination. Bivariate analyses followed by logistic regression models adjusted for relevant confounders were used to determine the independent effects of specific drug classes on outcomes of interest. **RESULTS:** Among 1490 completed pregnancies, there were 1431 live births. One-year infant outcomes were available in 1010. Exposure was to thiopurines (n = 242), biologics (n = 642), or both (n = 227) vs unexposed (n = 379). Drug exposure did not increase the rate of congenital malformations, spontaneous abortions, preterm birth, low birth weight, and infections during the first year of life. Higher disease activity was associated with risk of spontaneous abortion (hazard ratio, 3.41; 95% confidence interval, 1.51–7.69) and preterm birth with increased infant infection (odds ratio, 1.73; 95% confidence interval, 1.19–2.51). **CONCLUSIONS:** Biologic, thiopurine, or combination therapy exposure during pregnancy was not associated with increased adverse maternal or fetal outcomes at birth or in the first year of life. Therapy with these agents can be continued throughout pregnancy in women with IBD to maintain disease control and reduce pregnancy-related adverse events. ClinicalTrials.gov, Number: NCT00904878.

Keywords: Crohn's Disease; Ulcerative Colitis; Pregnancy.

Abbreviations used in this paper: **ASQ3, Ages and Stages Questionnaire, 3rd edition; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; LBW, low birth weight; OR, odds ratio; SAB, spontaneous abortion; TNF, tumor necrosis factor; UC, ulcerative colitis.**

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Incidence of inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC) is highest during reproductive years.[1] Compared with age-matched controls, pregnant women with IBD are more likely to experience spontaneous abortion (SAB), preterm birth, and complications during labor and delivery.[2] Active disease increases risk of adverse outcomes.[3] Therefore, medical therapy is required before and during pregnancy to maintain remission.

Therapy includes thiopurines (azathioprine, 6-mercaptopurine); biologics (monoclonal antibody), tumor necrosis factor (TNF) antagonists (infliximab, adalimumab, certolizumab pegol, golimumab), anti-integrins (vedolizumab, natalizumab), anti-interleukin 12/23 (ustekinumab), or combination of biologic and thiopurines. Fetal exposure of animals to supratherapeutic doses of thiopurines produce congenital malformations,[4] but human studies have not shown clear risk.[5,6] Biologics are immunoglobulins that are actively transported across the placenta by Fc receptors (FcRn) during the second and third trimester. They can persist in infants up to 9 months after birth.[7,8] The exception is certolizumab pegol, a Fab' fragment that passively crosses the placenta and is present in trivial concentrations at birth.[8] Despite current biologic safety data,[9] there remains hesitation about its use during pregnancy. Primarily, concerns remain regarding risk of congenital malformations and consequences of placental transfer on immune function. Recent data from France demonstrated increased maternal complications in IBD women receiving anti-TNF therapy (odds ratio [OR], 1.49; 95% confidence interval [CI], 1.31–1.67). However, therapy discontinuation before week 24 of gestation was associated with increased maternal disease but no reduction in maternal complications compared with continuation of therapy.[10] Current North American guidelines[11] and American Gastroenterological Association Care Pathway[12] recommend continuation of anti-TNF and thiopurine therapy throughout pregnancy, but acknowledge the low-quality evidence. In contrast, European guidelines suggest stopping biologics as early as 22 weeks' gestation,[13] despite a 10%–25% increased risk of disease flare[14] or loss of response to the agent. We performed a prospective cohort study at selected US centers to assess pregnancy outcomes after in utero exposure to thiopurines, biologics, and combination therapy, and measured maternal–infant placental transfer of monoclonal antibodies and infant achievement of developmental milestones.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Active inflammatory bowel disease in pregnancy can lead to adverse pregnancy and neonatal events including pregnancy loss and preterm birth. To maintain remission, medications need to be continued, however, the safety of biologics is not well established. This has led to drug discontinuation in pregnancy with subsequent increased flares and adverse neonatal outcomes. The aim of this study was to compare outcomes among pregnancies exposed versus unexposed in utero to biologics, thiopurines or a combination. Placental transfer was measured and developmental milestones among infants was assessed.

NEW FINDINGS

This was the largest prospective study of biologic safety in pregnancy with 1490 pregnant women, including 869 biologic exposed. There was no increase in adverse events based on drug exposure during pregnancy or placental transfer of biologics. Our data confirmed that disease activity increased spontaneous abortion and preterm birth increased infections. Developmental milestones out to one year were unaffected by drug exposure.

LIMITATIONS

The limitations include the self-reported nature of the data and lack of objective markers of disease activity. However, for many endpoints, patient reported outcomes are standard and the sites had access to medical records to confirm findings.

IMPACT

The findings of the study strongly support continuing biologic therapy throughout pregnancy given no increase in harm from drug exposure and clear evidence of adverse events with disease activity.

Methods

Study Design

The PIANO (Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes) study is a prospective observational study that enrolled pregnant women with IBD at 30 US centers between January 2007 and March 2019 (ClinicalTrials.gov, Number NCT00904878). We administered questionnaires at study intake (any point during pregnancy), each subsequent trimester; delivery; and 4, 9, and 12 months after birth. Offspring enrolled after 2010 were assessed for developmental milestones at 12, 24, 36, and 48 months after estimated due date.

Participants

Institutional Review Boards at each center approved the study and written informed consent was obtained. Only women with IBD and singleton pregnancies were eligible for inclusion.

Exposures

Demographic and disease-specific exposures. Using patient questionnaires and medical records, we collected maternal demographic variables (ie, age, marital status, smoking, and substance use) and IBD-related variables (ie, diagnosis, duration of disease, prior surgery, and disease location).

Medication use. Information was collected on medication use before conception, during pregnancy, and for 1 year postpartum. Exposure was defined as use of thiopurines or biologic in the 3 months before last menstrual period or any time during pregnancy. Women were assigned to 1 of 4 groups based on drug exposure: unexposed (includes mesalamine, corticosteroids, and antibiotics); thiopurine exposed; biologic exposed; and combination (both thiopurine and biologic) exposed. We repeated analyses evaluating only anti-TNFs, excluding other biologics.

Disease Activity

Disease activity was measured using the Harvey-Bradshaw Index[15] for CD and Simple Clinical Colitis Activity Index for UC.[16] In additional analyses, remission or mild disease was considered inactive and moderate or severe disease was considered active. A flare was further defined as score consistent with active disease and at least 1 of the following: new medication added, change in current prescription (ie increased dose), IBD-related surgery, or IBD-related hospitalization.

Pregnancy Outcomes

We collected pregnancy outcomes and complications of labor including: SAB, preterm birth (<37 weeks), stillbirth, intrauterine growth restriction, small for gestational age, low birth weight (LBW) (<2500 g), abruptio placenta, eclampsia/preeclampsia, cesarean section, and fetal distress.

Neonatal Outcomes

We collected infant outcomes by questionnaires. Height and weight percentiles were calculated at birth by Intergrowth-21st calculators, and then by World Health Organization curves. Very low for height or weight was defined as <25th percentile. Infant intensive care unit admission, congenital malformations, and maternal-reported infant infections were collected. Infections were categorized into serious infections (requiring hospitalization) or nonserious infection (any reported infection without hospitalization). Due to the frequency of otitis media in childhood, sensitivity analyses were repeated excluding this infection.

Developmental Milestones

Developmental milestones were assessed through the nationally validated Ages and Stages Questionnaire, 3rd edition (ASQ3),[17] at 12, 24, 36, and 48 months of age for patient subsets who reached these additional age milestones in the registry. Specific categories of milestones evaluated included communication, fine motor skills, gross motor skills, personal social, and problem solving.

Placental Transfer

We collected maternal, cord, and infant serum on the day of birth in a subset of maternal–child pairs on biologic agents. If the infant had detectable serum concentration at birth, additional samples were collected at months 3 and 6. Prometheus Biosciences or Sanquin Laboratories determined serum concentrations of all drugs.[18] As serum trough concentrations for various biologic agents are not well-established, for purposes of analysis we considered a trough concentration of 0–3 to be low, 3–10 therapeutic, 10–20 high, and >20 very high. Drug concentration at birth was analyzed as both a continuous variable as well as by category, overall and for each biologic class.

Outcomes

The primary outcomes of the study were rates of congenital malformations, SAB, preterm birth, LBW, and infections (serious and nonserious) in the 3 exposure groups, relative to the unexposed group. We also aimed to determine differences in infant developmental milestones at 12 months of age by drug exposure and to correlate infant serum drug exposure data with infectious complications in the first year of life.

Statistical Analysis

We examined univariate and bivariate distributions of all exposures and outcomes. We compared incidence or birth prevalence of pregnancy and neonatal outcomes among women in the thiopurine, biologic, and combination therapy exposure groups relative to the same outcomes among women exposed to neither thiopurines nor biologics. We calculated crude ORs, and then adjusted for relevant confounders such as disease activity, maternal characteristics (eg, age and smoking), prior SAB, and infant characteristics (preterm birth), if applicable. For analyses of SAB, we limited the cohort to those enrolled before 20 weeks' gestation. We used Cox proportional hazard models to determine factors associated with SAB by 20 weeks, including medication exposures, maternal age, disease activity, and prior SAB. For analyses of infant infections (serious, nonserious, or any infection), we divided biologics into anti-TNF–treated women alone, and individually assessed the risk with the 3 most common agents—infliximab, adalimumab, and certolizumab pegol. For developmental milestones, we compared mean scores on each milestone by drug exposure category to unexposed IBD referent and the general population mean by t test. Bivariate statistics were used to determine whether maternal or infant exposures were associated with any one low-scoring domain on developmental milestones. Weight and height percentiles were also compared across drug exposure groups using bivariate analyses. We calculated ORs of <25% for length or weight by drug exposure class, adjusted for maternal age and highest disease activity during pregnancy. For the subset with placental transfer data available, we reported mean drug concentrations for cord, maternal, and baby serum, as well as distribution of concentrations. Spearman's ρ and Kruskal-Wallis χ^2 test statistics were used to analyze associations between serum drug concentrations and outcomes of interest as continuous drug concentrations and by category. As missing data were rare, a complete case analysis is presented as the primary analysis. Data were analyzed using SAS, version 9.2 (SAS Institute).

Results

Of 1712 patients enrolled, 1490 completed pregnancies, with 1431 live births. One-year measurements were available in 1010 offspring. Table 1 reports maternal demographic characteristics. Among 30 centers, the estimated gestational age at enrollment was a median of 115 days (interquartile range, 70–172 days). Of 869 women with exposure to biologic (51 exposed to more than 1) or combination therapy, 421 were infliximab, 279 were adalimumab, 135 were certolizumab pegol, 11 were golimumab, 15 were natalizumab, 41 were vedolizumab, and 18 were ustekinumab. Individuals with CD were less likely unexposed vs UC (16% vs 41%; $P < .0001$), and more likely to be on biologics (51% vs 30%; $P < .0001$) or combination therapy (18% vs 11%; $P < .001$). There were no differences in rates of thiopurine use (15% vs 18%; $P = .30$) for CD vs UC.

Table 1. Characteristics of Entire Cohort by Drug Exposure Class

Variable	Overall (n = 1490)	None (n = 379)	Biologics[a] (n = 642)	Thiopurine[b] (n = 242)	Combination[c] (n = 227)	*P* value
Maternal age at delivery, *y*, mean (SD)	32.0 (4.6)	32.5 (4.6)	31.8 (4.5)	31.9 (4.7)	31.6 (4.5)	.07
Total pregnancies, including current, mean (SD)	2.1 (1.3)	2.2 (1.3)	2.1 (1.3)	2.1 (1.4)	2.0 (1.2)	.18
Disease duration, *y*, median (IQR)	8.3 (4.4–13.0)	7.1 (2.9–12.6)	8.7 (4.8–13.3)	8.5 (4.7–12.4)	8.7 (5.4–13.6)	.001
Body mass index,[d] kg/m^2, mean (SD)	24.9 (4.8)	24.9 (4.3)	25.0 (4.9)	24.2 (4.5)	25.2 (5.1)	.46
Disease status, n (%)						<.001
CD	921 (62)	147 (39)	471 (74)	137 (57)	123 (71)	
UC	535 (36)	218 (58)	137 (23)	98 (40)	47 (27)	
IBD-unclassified	34 (2)	14 (4)	8 (1)	7 (3)	3 (2)	
Smoking status, n (%)						.53
Current	23 (2)	4 (1)	11 (2)	5 (2)	3 (1)	
Former (before pregnancy)	308 (22)	75 (21)	137 (23)	57 (25)	38 (18)	
Never	1057 (76)	272 (77)	451 (75)	163 (72)	169 (80)	
Alcohol use, n (%)						.02
Current	146 (11)	28 (8)	59 (10)	22 (10)	37 (18)	
Former (before pregnancy)	855 (62)	220 (63)	381 (64)	139 (61)	115 (55)	
Never	384 (28)	103 (29)	156 (26)	65 (29)	57 (27)	
Recreational drug use, n (%)						.42
Current	1 (0.)	1 (0.3)	0 (0)	0 (0)	0 (0)	
Former (before pregnancy)	65 (5)	22 (6)	26 (4)	10 (4)	7 (3)	
Never	1321 (95)	327 (93)	573 (96)	216 (96)	202 (97)	

[a]Biologics defined as anti-TNF, anti-integrin, and anti–interleukin-12/23.
[b]Thiopurine (azathioprine or 6-mercaptopurine).
[c]Combination defined as biologic plus thiopurine.
[d]Prepregnancy body mass index as reported at intake.

Table 2. Pregnancy-Related Complications by Drug Exposure, Controlling for Maternal Age, Steroid Use, and Disease Activity

Event	No exposure (n = 379)	Biologics,[a] OR (95% CI) (n = 642)	Thiopurine,[b] OR (95% CI) (n = 242)	Combination,[c] OR (95% CI) (n = 227)
Any pregnancy complication[d]	1.0 (ref)	1.2 (0.8–1.7)	1.3 (0.8–2.0)	0.8 (0.5–1.3)
SAB (only gestation ages ≤140 d)	1.0 (ref)	1.3 (0.5–3.3)	1.4 (0.4–4.2)	1.2 (0.4–3.8)
SAB (all gestation ages)	1.0 (ref)	1.3 (0.5–3.0)	1.3 (0.4–3.8)	1.1 (0.3–3.3)
Preterm birth (<37 wk)	1.0 (ref)	0.9 (0.5–1.5)	1.4 (0.8–2.6)	1.8 (1.0–3.3)
Small for gestational age	1.0 (ref)	1.1 (0.5–2.0)	0.5 (0.2–1.5)	0.7 (0.3–1.8)
LBW (<2500 g)	1.0 (ref)	1.0 (0.5–1.8)	0.6 (0.3–1.5)	1.2 (0.6–2.5)
Intrauterine growth restriction	1.0 (ref)	0.6 (0.2–1.4)	0.3 (0.07–1.5)	0.7 (0.2–2.3)
Cesarean section	1.0 (ref)	1.3 (1.0–1.8)	1.3 (0.9–1.9)	1.7 (1.1–2.5)
NICU at birth	1.0 (ref)	1.1 (0.7–1.9)	1.2 (0.6–2.2)	1.5 (0.8–2.8)
Congenital malformations	1.0 (ref)	1.5 (0.9–2.5)	1.4 (0.8–2.7)	1.6 (0.8–3.1)
Any of the above	1.0 (ref)	1.5 (1.1–2.0)	1.6 (1.1–2.3)	1.4 (0.9–2.0)
Any of the above without considering cesarean section	1.0 (ref)	1.2 (0.9–1.6)	1.4 (1.0–2.0)	1.2 (0.8–1.8)

NOTE. Logistic regression models controlling for maternal age, steroid use, and disease activity.
NICU, neonatal intensive care unit.
[a]Biologics defined as anti-TNF, anti-integrin, and anti–interleukin-12/23.
[b]Thiopurine (azathioprine or 6-mercaptopurine).
[c]Combination defined as biologic + thiopurine.
[d]Defined as any self-reported pregnancy complication (excludes intrauterine growth restriction, cesarean section, or pre-term delivery).

Pregnancy Outcomes

There were 133 infants (9%) with congenital malformations, 42 SABs (3%), 91 LBWs (7%), and 132 preterm births (10%). There were 58 small-for-gestational-age infants (4%), 30 intrauterine growth restrictions (2%), 5 stillbirths (0.30%), 613 cesarean sections (44%), 137 neonatal intensive care unit stays (10%), and 280 patients (20%) with at least 1 self-reported pregnancy-related

Table 3. Rates of Infection During the First 12 Months of Life by Drug Exposure Among Live Births

Variable	Overall, n/N (%) (n = 1,431)	No exposure, n/N (%) (n = 366)	Biologics,[a] n/N (%) (n = 616)	Thiopurine,[b] n/N (%) (n = 233)	Combination,[c] n/N (%) (n = 216)	*P* value
Infection at birth						
Serious	29/1384 (2)	3/348 (1)	15/601 (2)	6/227 (3)	5/ 208 (2)	.27
Infection by 4 mo of life						
Serious	37/1103 (3)	7/278 (3)	19/479 (4)	8/ 183 (4)	3/163 (2)	.41
Nonserious	175/1103 (16)	38/278 (14)	89/479 (19)	26/183 (14)	22/163 (13)	.19
Any infection[d]	191/1103 (17)	42/278 (15)	95/479 (20)	32/183 (17)	22/163 (13)	.19
Infection in the first year of life						
Serious	79/1431 (6)	18/366 (5)	35/616 (6)	18 /233(8)	8/216 (4)	.28
Nonserious	637/1431 (43)	165/366 (44)	268/616 (43)	103/233 (44)	102/216 (47)	.79
Any infection[d]	658/1431 (46)	173/366 (47)	277/616 (45)	107/233 (46)	102/216 (47)	.87

[a]Biologics defined as anti-tumor necrosis factor–α, anti-integrin, and anti–IL-12/23.
[b]Thiopurines (azathioprine or 6-mercaptopurine).
[c]Combination defined as biologic plus thiopurine.
[d]Any infection defined as any serious (infection requiring hospitalization) or non-serious infection (maternal reported infection not requiring hospitalization)

Table 4. Subset With Maternal, Cord, and Infant Serum Drug Concentrations at Time of Delivery (n = 235)

Variable	Infliximab	Adalimumab	Certolizumab pegol	Golimumab	Vedolizumab	Natalizumab	Ustekinumab
n	99	66	33	4	22	4	7
Infant concentration, μg/mL, median (range)	27.1 (0.1–103.1)	9.4 (2.5–26.0)	0.0 (0.0–0.0)	2.2 (0.0–4.1)	8.2 (0.0–22.0)	3.8 (3.7–3.9)	5.0 (0.6–8.7)
Infant or cord concentration, μg/mL, median (range)[a]	28.5 (0.0–110.1)	9.1 (0.0–26.0)	0.0 (0.0–5.1)	3.4 (1.1–4.1)	8.9 (3.0–22.0)	1.8 (0.0–3.9)	5.0 (0.6–40.0)
Maternal concentration, μg/mL, median (range)	12.0 (0.0–129.3)	8.2 (0.0–39.8)	25.0 (0.0–56.4)	2.2 (0.5–3.7)	13.0 (0.4–44.0)	2.5 (0.0–5.5)	4.0 (0.1–18.9)
Infant or cord/maternal concentration ratio, median (range)[b]	2.4 (0.7–8.0)	1.3 (0.4–5.4)	0.0 (0.0–0.1)	1.5 (0.0–2.2)	0.5 (0.0–1.7)	0.7 (0.7–0.7)	1.4 (0.7–13.7)
Days since last maternal dose, median (range)	50.0 (6.0–133.0)	14.0 (1.0–150.0)	13.0 (2.0–30.0)	21.0 (18.0–28.0)	29.0 (1.0–84.0)	32.5 (6.0–141.0)	35.0 (7.0–74.0)
Infant concentration >10 μg/mL, n (%)[c]	85/98 (87)	20/65 (31)	0/33 (0)	0/4 (0)	9/22 (41)	9/22 (41)	1/7 (14)
Maternal concentration >10 μg/mL, n (%)[c]	54/95 (57)	20/65 (31)	30/33 (91)	0/4 (0)	12/22 (55)	0/4 (0)	1/7 (14)
Maternal concentration >10 μg/mL despite held dose, n (%)[d]	7/32 (22)	3/23 (13)	1/1 (100)	—	0/ 3 (0)	0/2 (0)	1/ 3 (33)
Infant concentration at subsequent blood draw,[e] μg/mL, median (range)	0.6 (0.0–7.0)	0.0 (0.0–2.2)	0.0 (0.0–0.0)	—	0.0 (0.0–0.0)	—	0.1 (0.0–0.2)

[a]Infant concentration; if missing, then cord concentration.
[b]Ratio only computed when maternal concentration is >0.
[c]Defined as >10 μg/mL; note that this is the level used for analysis for all biologics.
[d]Only for those with days since last maternal dose as follows: >14 for adalimumab, >28 for natalizumab, certolizumab pegol and golimumab, and >56 for infliximab, vedolizumab, and ustekinumab.
[e]Among those with infant samples available, first subsequent level at a median of 129.5 days after delivery.

Table 5. Comparison of Drug Exposure During Pregnancy on Childhood Developmental Milestones at 12 Months[a] (n = 411)

	Unexposed		Biologics[b]				Thiopurines[c]				Combination[d]			
Milestone	n	Mean	n	Mean	Δ	*P* value	n	Mean	Δ	*P* value	n	Mean	Δ	*P* value
Communication	92	50.6	206	52.5	1.9	.12	52	50.7	0.1	.97	62	52.8	2.2	.17
Fine motor	92	55.7	205	56.3	0.6	.46	52	57.1	1.4	.15	62	55.9	0.2	.87
Gross motor	92	49.8	206	53.0	3.2	.06	52	50.0	0.2	.96	61	51.3	1.5	.52
Personal-social	92	48.6	205	52.1	3.5	.01	52	49.7	1.1	.58	62	51.3	2.7	.12
Problem solving	92	51.0	204	53.2	2.2	.10	52	53.1	2.1	.20	62	53.0	2.0	.24

[a]Calculated using ASQ3; premature infants were only included if their questionnaire window correlated with the window for their adjusted age (based on due date) rather than birth date.
[b]Biologics defined as anti-TNF, anti-integrin, and anti–IL-12/23.
[c]Thiopurine (azathioprine or 6-mercaptopurine).
[d]Combination defined as biologic plus thiopurine.

complication (excluding cesarean section, intrauterine growth restriction, or preterm delivery). There were overall no differences in rates of pregnancy complications by drug class, although women on biologics and combination therapy had higher rates of cesarean sections compared with the unexposed population (Table 2, Supplementary Appendix). No pattern of congenital malformations suggests an association for a specific drug or disease type (CD or UC) (Supplementary Appendix).

Analyzing those entering the cohort before 20 weeks, the rate of SAB was 41 of 944 (4%). In a Cox model for SAB censored at 20 weeks' gestation, maternal age (hazard ratio [HR], 1.03; 95% CI, 0.96–1.11) and drug class were not predictive of SAB (biologic HR, 1.20; 95% CI, 0.50–2.90; thiopurine HR, 0.96; 95% CI, 0.28–3.33; combination HR, 0.96; 95% CI, 0.28–3.33). Active disease (HR, 3.41; 95% CI, 1.51–7.69) and prior SAB (HR, 2.17; 95% CI, 1.05–4.49) were independently associated with SAB before 20 weeks.

Infections

We found no increase in serious, nonserious, or any infection in the first year of life. (Table 3). No significant difference in infectious outcomes was found when analyses were repeated excluding otitis media, preterm birth, limiting biologic exposure to only anti-TNF agents, or when each anti-TNF agent was excluded individually. Infection rates did not differ by individual biologic agent (Supplementary Appendix). Controlling for preterm birth, maternal age, and disease activity, use of biologic (OR, 0.92; 95% CI, 0.70–1.20), thiopurine (OR, 0.90; 95% CI, 0.64–1.28), or combination therapy (OR, 0.93; 95% CI, 0.66–1.32) was not associated with increased risk of any infection in the first year of life. Preterm birth was the only independent risk factor for infection (OR, 1.73; 95% CI, 1.19–2.51). The majority of infections were nonserious, consisting primarily of otitis media and upper respiratory infections. Serious infections were rare, consisting of febrile illnesses requiring hospitalization and antibiotics and sepsis.

Disease Activity

Mothers with UC had significantly lower rates of remission per trimester compared with mothers with CD ($P = .002$ trimester 1, $P < .0001$ trimesters 2 and 3). In addition, there were significantly higher rates of flares for UC compared with CD. There were no differences in postpartum flares. When evaluating flare by pregnancy trimester, a significantly greater percentage of women with IBD who had flares in the first and third trimester and postpartum were not on biologic agents or immunomodulators (Supplementary Appendix). For women who were on biologics during pregnancy, we also evaluated timing of biologic agents and subsequent flares. Discontinuation of a biologic in the third trimester was not associated with an increased risk of subsequent flare postpartum (Supplementary Appendix*D*). A significantly higher percentage of women exposed to more than 1 biologic experienced a flare during pregnancy compared with those on only a single biologic (47% vs 20%; $P = .001$). The vast majority of women (81%) exposed to more than 1 biologic switched within the anti-TNF class.

Infant Growth

Infants of mothers receiving thiopurines or combination therapy had significantly increased birth weight. Otherwise, there were no differences in height or weight outcomes by drug exposure (Supplementary Appendix), or in odds of being very low for length or weight, controlling for preterm birth and maternal disease activity (Supplementary Appendix).

Serum Drug Concentrations

In the subset with biologic serum concentration data (Supplementary Appendix), the greatest number (n = 99) were exposed to infliximab, followed by adalimumab (n = 66), certolizumab pegol (n = 33), vedolizumab (n = 22), ustekinumab (n = 7), natalizumab (n = 4), and golimumab (n = 4). The highest infant and cord serum concentrations at birth were with infliximab, with certolizumab pegol having the lowest. For all biologics except certolizumab pegol, infants had detectable concentrations at delivery, most at levels higher than the mother (Table 4) By a median of 129.5 days (range, 81–242 days) after delivery, at time of first subsequent infant drug level, 86.8% had a concentration <2.0 μg/mL. We evaluated risk of serious infection or any infection in the first 12 months by birth serum drug concentration and found no differences (Supplementary Appendix).

Developmental Milestones

Infant developmental milestones by drug exposure are reported in Table 5. There were no differences in developmental milestones in the first year of life by exposure status within the cohort or compared with validated population norms (ASQ3). Developmental milestones to 48 months are in Supplementary Appendix.

Discussion

In this prospective cohort of pregnant women with IBD, the use of biologic and thiopurine therapy, alone or in combination, was not associated with an increase in congenital malformations, SAB, preterm birth, LBW, or infections in the first year of life. However, maternal disease activity was associated with SAB and preterm birth with infant infections.

Multiple smaller studies support our findings, with no reported increase in congenital malformations with anti-TNF use in pregnancy.[19–22] The rate of SAB in our cohort was lower than the general population. However, SAB is inherently difficult to study, as it can occur early in pregnancy before the woman is aware of the pregnancy or reports it to her provider. Maternal disease activity and prior SAB were significant risk factors for SAB in this cohort. Other studies have reported preterm birth to be increased with maternal disease activity.[23] In our cohort, preterm birth was associated with increased infant infections.

Overall, these findings emphasize the need to control disease activity during pregnancy, as well as the lack of harm associated with the use of biologic and thiopurine therapy.

As noted in other studies,[14] UC patients had significantly increased disease activity compared with CD during each trimester. This may be due to production of pro-inflammatory cytokines by the placenta that activate UC,[24] or because UC activity is undetected and undertreated in pregnant women. In this cohort, 43% of UC women were unexposed to biologics or thiopurines, despite higher rates of disease activity, whereas only 19% of women with CD were unexposed. Women who were unexposed to biologics or immunomodulators were more likely to flare during the course of pregnancy. This demonstrates the need for therapy to maintain control of inflammation throughout pregnancy. Preconception counseling on medication use during pregnancy could improve these outcomes. In addition, women exposed to more than 1 biologic during pregnancy had higher rates of disease flare. Although the directionality of this cannot be determined from the data, it is presumed that therapy was changed because of active disease, rather than that disease activity was a result of a change in therapy.

Practitioners have generally become more comfortable using biologics in the first trimester of pregnancy. However, as significant placental transfer occurs, there have been lingering concerns about infection and altered immune development in infants when biologics are used in the third trimester. The European guidelines[13] recommend cessation of biologics as early as week 22 of gestation, despite the risk of increased disease activity in the mother.[10] We found that neither combination therapy nor monotherapy with any biologic increased the risk of infections at 1 year, after accounting for disease activity and preterm birth. Preterm delivery was the only factor independently associated with increased infant infections.[12] There is no strong rationale to withhold biologic therapy in any pregnant IBD patient based on available evidence from PIANO and other international studies.

In a subset of infants followed for up to 48 months, drug exposure during pregnancy was not associated with differences in developmental milestones as measured by ASQ3, suggesting biologic and thiopurine exposure does not adversely affect infant neurodevelopment. Socioeconomic factors are influential in developmental milestones and our cohort has high income and education levels. However, within the exposure groups in the cohort, there was no reduction in achievement of milestones.

There are a number of strengths to this study. The large sample of women with IBD followed prospectively throughout pregnancy and the first 4 years of the infant's life increases the precision of our estimates. Detailed prospective data collection allowed for documentation of disease activity, medication and disease state changes, and complications to both mother and child. The limitations include the self-reported nature of the data and lack of objective markers of disease activity. It is possible that there is misclassification bias, as data are reported by mothers rather than ascertained from the medical record. However, self-report is the reference standard for instruments such as ASQ3 and the basis of patient-reported outcome measures of disease activity in IBD. It is also unlikely that this bias would be differential by specific class of therapy. Objective measures were used whenever possible, such as calculation of LBW based on infant's actual weight and preterm birth based on gestational age. Given the observational nature of the data, selection bias is possible due to loss of follow-up. However, loss of follow-up was not different by drug class, suggesting that this would be a nondifferential bias, if present.

Biologic, thiopurine, and combination therapy exposure during pregnancy in women with IBD was not associated with increased maternal or infant adverse events in the first year of life. Maternal disease activity was an independent risk factor for SAB and preterm birth increased the risk of infant infections. Practitioners should continue biologic and/or thiopurine therapy throughout pregnancy given no evidence of increase in harm from drug exposure and the clear association of active disease with adverse events.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dxdoi.org/10.1053/j.gastro.2020.11.038.

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Conflicts of interest
The authors disclose the following: Uma Mahadevan serves as a consultant for Abbvie, Janssen, Pfizer, Prometheus biosciences, Gilead, UCB and Takeda. Millie Long serves as a consultant for AbbVie, Takeda, UCB, Pfizer, Janssen, Prometheus, and Salix. She receives grant support from Pfizer and Takeda. Abhik Roy reports no conflicts. Christina Chambers receives research funding from Janssen Pharmaceuticals; Pfizer, Inc.; Takeda Pharmaceutical Company Limited; UCB Pharma, USA and the Gerber Foundation. Bruce Sands receives consulting fees from Abbvie, Janssen, Pfizer, Prometheus Laboratories, Shire, Takeda; honoraria for speaking in CME programs from Takeda, Janssen, Pfizer; and research funding from Pfizer, Takeda, Janssen. Russ Cohen: serves on the speaker's Bureau (disease-state only; not promotional drug talks) for Abbvie and Takeda; serves as Consultant / Advisory/ Scientific Advisory Board for Abbvie Laboratories, Janssen, Pfizer, Takeda, UCB Pharma; receives research support from Abbvie; Pfizer; Takeda Pharma; UCB Pharma, Marla Dubinsky receives grant support from Janssen, Abbvie, Pfizer, Prometheus biosciences and serves as a consultant for Abbvie, Janssen, Pfizer, Prometheus biosciences, Takeda. Sunanda Kane serves as a consultant for Pfizer. William Sandborn receives research grants from Abbvie, Janssen, Pfizer, Prometheus Biosciences, Shire, Takeda; Consulting fees from Abbvie, Bausch Health (Salix), Janssen, Pfizer, Prometheus Biosciences, Shire, Takeda, UCB; Stock or stock options from Prometheus Biosciences; and Spouse: Prometheus Biosciences - employee, stock, stock options; Prometheus Laboratories – stock, stock options, consultant.

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